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Medicinal plants with analgesic and antipyretic effects

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Abstract

Pain is an unpleasant psychological and emotional state associated with tissue damage. While, fever is a secondary effect of infection, tissue damage, inflammation, graft rejection, tumors and other pathological states. The current review highlighted the medicinal plants possessed analgesic and antipyretic effects.

Keywords: Medicinal Plants; Analgesic; Antipyretic; Pain; Fever; Mechanism

1. Introduction

Pain is an unpleasant psychological and emotional state associated with tissue damage. It is mediated by many mediators (prostaglandins, cytokines, histamine, serotonin, substance P, capsaicin, and nitric oxide) an created by different reasons (harmful heat, stretch, electrical flow, necrosis, inflammation, laceration and spasm)[1-2]. Many medicinal plants have exhibited analgesic activities [3-4], and they have produced their effect through various mechanisms including: inhibition of arachidonic acid release [5], inhibition of nitric oxide and COX synthesis [6], inhibition of cyclooxygenase enzyme activity and subsequent inhibition of prostaglandin synthesis [7-9], enhancement of endogenous opioid transporters of the central nervous system [10], stimulatory effect of GABA A receptors [11], binding to pain receptors, effect on ligand-sensitive channels, reduction of sodium influx and inhibition of the release of various mediators [8, 12].

On the other hand, fever is a secondary effect of infection, tissue damage, inflammation, graft rejection, tumors, or other pathological conditions. The infected or damaged tissue initiates the formation of inflammatory mediators (like interleukin 1β, and TNF-α), which in turn increase the synthesis of prostaglandin E2 near preoptic hypothalamus area and trigger the hypothalamus to elevate the body temperature[13]. Many medicinal plants possess antipyretic activity by inhibiting prostaglandin production or by inhibiting the production and/or activity of inflammatory mediators [14-16]. This review is designed to highlight medicinal plants with analgesic and antipyretic effects.

2. Medicinal plants with analgesic and antipyretic effects

2.1. Althaea officinalis

Hypolaetin 8-glucoside isolated from *Althaea officinalis* has been tested for analgesic activity in rats. This flavonoid (30, 60 and 90 mg/kg, ip) showed analgesic activity lower than the one of phenylbutazone. However, hypolaetin 8-glucoside was also more potent than flavonol, troxerutin (both at the doses of 100, 200, 300 and 400 mg/kg, sc)[17-18].

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2.2. Adiantum capillus-veneris

The analgesic activity of the ethanolic extract of *Adiantum capillus-veneris* and its fraction was tested by tail flick method and writhing test, the result showed significant analgesic activity with insignificant gastric ulceration as compared to the standard anti-inflammatory analgesic antipyretic drugs [19-21].

2.3. Alhagi maurorum

The aqueous extract of *Alhagi maurorum* was evaluated in mice at doses of 125, 250 and 500μg/animal, for its analgesic effects. The analgesic effect of the aqueous extract of *Alhagi maurorum* at doses of 125, 250 and 500μg/animal and diclofenac sodium(1μg/animal. The extracts induced analgesic effects and the dose of 500μg/ animal, showed the most potent effect [22-23].

The antinociceptive effect of methanolic extracts (200 and 400 mg/ kg) of *Alhagi maurorum* was studied using acetic acid-induced writhing and tail-flick test in mice. Oral administration of methanolic extracts of *Alhagi maurorum* significantly inhibited the nociception to acetic acid-induced writhe even in low dose. In the tail-flick test, methanolic extracts of *Alhagi maurorum*in a dose of 400 mg/ kg produced significant increase in the latency to response of tail to thermal stimulation [24].

2.4. Ailanthus altissima

Ailanthus altissima stem bark of Egyptian origin were evaluated for their analgesic, antipyretic and antiulcer activities. Analgesic and antipyretic activities were evaluated by hot plate test at doses of 50 mg/ kg and 100 mg/kg of the extracts. The extracts have similar analgesic activity and the ether extract showed good analgesic activity at 30min. Also extracts showed a decrease on rectal temperature that means an hypothermic activity of the plant extracts with longer effect for the ether extract. Ether extracts showed a gastric ulcer protection activity and cytoprotection activity in a doses of 100 mg/kg as well as 50 mg/kg in ethanol induced ulcer in mice [25-26].

2.5. Allium cepa

Hot plate and formalin tests were used to study the analgesic effect of fresh onion juice (7.5 ml/kg) in mice during acute and chronic pain stages modeling. A significant analgesic property for fresh onion juice in both pain phases was recorded, the effect was similar to that of morphine (5 mg/kg). Fresh onion juice also decreased the hind paw thickness significantly. In the mean time, it also demonstrated better results than the standard treatment, diclofenac[27-28].

2.6. Alpinia galanga

A significant analgesic effect in formalin test was produced bytopical preparation containing methanolic extract of *Alpinia galanga* rhizome [29-30].

2.7. Ammannia baccifera

The ethanolic extract of the *Ammannia baccifera* (whole plant) at doses of 200, 400 and 600mg/kg, ip produced an inhibition of 20.7%, 43.4% and 72.9%, respectively, of the abdominal writhes induced by acetic acid in mice. In the formalin test, the administration of 200,400 and 600mg/kg, ip had no effects in the first phase (5 min) but produced a dose dependent analgesic effect on the second phase (1540 min) with inhibitions of the licking time of 27.3%, 47.7% and 57.4%, respectively [31-32]. The methanolic extract exhibited significant analgesic activities at the dose of 100 and 200 mg/kg, po. The analgesic effect of the higher dose of the extract (200 mg/kg) was comparable with the standard drugs aspirin and morphine [33].

2.8. Anethum graveolens

A 10% aqueous extract of the fruits and 5% aqueous solution of the essential oil had analgesic effects in mice pain induced by hot plate and acetic acid writhing models. The effect of the fruits (1.0 g/kg) was comparable to 200 mg/kg of acetyl salicylic acid [43-35].

2.9. Arachis hypogaea

Cho-K1 cells stably transfected with opioid receptor subtypes μ, Δ, and κ was used to assay the affinity of peanut constituents to opioid receptors. Compound GC-143-8 was run in competition binding against all three opioid subtypes (μ, κ, and Δ). One of peanet stilbenoids showed opioid recetor affinity . Combined use of this compound and analgesic agents resulted in lower amounts of the latter needed to block pain [36-37].

2.10. Asclepias curassavica

The analgesic (flick method on mice) and antipyretic (Brewer's yeast induced pyrexia in rats) effects of the alcoholic and aqueous extracts of the stem of the plant were studied. The aqueous and alcoholic extracts of stem of *Asclepias curassavica* showed significant anti-pyretic and analgesic activity[38-39].

2.11. Astragalus hamosus

The analgesic effects of chloroform, hexane, ethyl acetate and aqueous fractions were evaluated by the hot-plate method. The hydroalcoholic extract of *Astragalus hamosus* possessed significant anti-nociceptive effects on both animal models. The findings showed that the hydroalcoholic extract at doses of 700 and 1000 mg/kg produced analgesic effects comparable to sodium salicylate. The hexane and ethyl acetate (but not the other fractions) showed significant analgesic activity in hot plate test, when compared to morphine [40-41].

2.12. Bidens tripartita

An aqueous infusion of aerial parts *Bidens tripartita*. was investigated analgesic effect.Infusion doses of 20ml/kg exhibited significant analgesic properties in a hot-plate test and antipyretic properties in carrageenan-induced local hyperthermia in rats. The effects were dose-dependent [42-43].

2.13. Caesalpinia crista

The analgesic effect of the ethanolic seed extract of *Caesalpinia crista* was investigated by writhing reflexes and tail immersion method in mice. The extract also showed potent analgesic activity 71% at 300 μg/ml by writhing reflexes in mice, and the tail withdrawal latency of mice was 5.30±0.05 sec at 300 μg/ml by tail immersion method. On the other hand, *Caesalpinia crista* seed coat extracted by 95% ethanol was screened for analgesic activity using hot plate test and tail immersion method. It appeared that seed coat extract has the ability to increase the pain threshold of the animals, reduce the pain factor and induce analgesia [44-46]. The analgesic and antipyretic activity of *Caesalpinia crista* seed oil were determined in experimental animal model (hot plate and yeast-induced pyrexia) at a dose of 100, 200 and 400 mg/kg orally. Pyrexia and writhes were reduced significantly ($P<0.05$) in *Caesalpinia crista* treated rats as compared to that of control [47-48].

2.14. Calendula officinalis

The analgesic effects of *Calendula officinalis* was evaluated in thermal pain threshold in male rats. *Calendula officinalis* extract significantly increased the tail flick latency compared to the control group ($P<0.05$), indicating that the extract reduced pain threshold [49-50].

2.15. Calotropis procera

The latex protein fraction administered intraperitoneally to male mice at doses of 12.5, 25 and 50 mg/kg showed a dose-dependent antinociceptive effect compared with the controls. Inhibition of the acetic acid induced abdominal constrictions was observed at doses of 12.5 mg/kg (67.9 %), 25 mg/kg (85 %) and 50 mg/kg (99.5 %) compared with controls. Latex protein at doses of 25 mg/kg (39.8 %; 42 %) and 50 mg/kg (66.6 %; 99.3 %) reduced the nociception produced by formalin in the 1st and 2nd phases, respectively, and this effect was not reversed by pretreatment with naloxone (1 mg/kg). In the hot plate test, an increase in the reaction time was observed only at 60 min after treatment with latex at doses of 25 mg/kg (79.5 %) and 50 mg/kg (76.9 %), compared with controls. Naloxone was unable to reverse this effect. The antinociceptive effects of protein fraction of the latex of *Calotropis procera* didn't depend of the opioid system[51]. A single oral dose of dry latex ranging (165 to 830 mg/kg) produced significant dose-dependent analgesic effect against acetic acid-induced writhing. The effect of a dose of 415 mg/kg was more pronounced than a 100 mg/kg oral dose of aspirin. Dry latex (830 mg/kg) produces marginal analgesia in a tail-flick model which was similar to that of aspirin [51]. The ethanol extract of *Calotropis* produced significant reduction of yeast induced increase in body temperature. There was a significant increase in reaction time of the treated mice placed on hot plate confirming analgesic activity of the extract [51]. The ethanolic extract of the aerial parts also possessed antipyretic effect. Administration of yeast produced an increase in rectal temperature from 97.32 ± 0.19oF which reached to its maximum in 4 h (100.02 ± 0.27oF). Administration of dry latex (DL)-250 mg/kg and 500 mg/kg at 4 h produced a significant ($P <0.05$) decline in rectal temperature to 98.50 ± 0.29oF and 98.45 ± 0.60^{o}F respectively. The antipyretic effect was compared with that of aspirin, which was found to be more potent and brought down the temperature to 96.9 ±0.38 ^{o}F ($P<0.001$) [51-52].

2.16. Canna indica

The effect of benzene and methanolextracts of various parts of *Canna indica* on nociceptive response using writhing test and hot plate method in mice was examined. All the extracts of *Canna indica* showed significant central and peripheral analgesic activity in hot plate method and acetic acid-induced writhing test, respectively, at the dose of 50 mg kg(-1) intraperitoneally. Methanolic extract of leaves of *Canna indica* showed highest increase in reaction time in hot plate method while benzene extract of leaves of *Canna indica* showed more inhibitory effect on writhing induced by acetic acid [53-54].

2.17. Capsicum annuum and Capsicum frutescens

Capsaicin reacts to transient receptor potential vanilloid 1 (TRPV1), previously known as the vanilloid receptor, which is mainly expressed in the sensory neurons. TRPV1 contained 838 amino acids and has a molecular weight of 95 kDa in both humans and rats, consisting of six transmembrane domains with a short pore-forming region between the fifth and sixth transmembrane domains. It was non-selective, ligand-operated cationic channel located primarily in the small fibers of nociceptive neurons. TRPV1 was also distributed in tissues of the brain, bladder, kidneys, intestines, liver, polymorphonuclear granulocytes, mast cells, keratinocytes, glial cells, and macrophages. It couples with a non-specific cation channel permeable to sodium and calcium ions, and is located in the plasma membrane and the endoplasmic reticulum where regulates intracellular calcium levels. Binding of capsaicin with TRPV1 increases intracellular calcium, triggering release of substance P and the calcium gene-related peptide (CGRP). Contact between capsaicin and sensory neurons produces pain, inflammation and a localized heat sensation. When applied locally to skin, it promotes an analgesic response due to desensitizing of the sensory neurons caused by substance P depletion [55-60]. Capsaicin and its analogues were used topically to treat chronic pain syndromes musculoskeletal pain, osteoarthritis, rheumatoid arthritis, post-herpetic neuralgia and diabetic neuropathy [61-63]. Topical application of capsaicin evokes burning pain, neurogenic inflammation (vasodilatation and plasma extravasation), and hyperalgesia to heat and mechanical stimuli [64-65]. The treated area becomes less sensitive to pain, after repeated applications, this effect made capsaicin a peripherally acting analgesic in chronic painful complains [66-67]. The sensory dysfunction after capsaicin application to the skin resulted from rapid degeneration of intracutaneous nerve fibers.The effect of intradermal injection of capsaicin on morphological changes in cutaneous nerve fibers that would account for its analgesic properties was studied by comparing cutaneous innervation in capsaicin-treated skin with psychophysical measures of sensation. At various times after capsaicin injection, nerve fibers were visualized immunohistochemically in skin biopsies and were quantified. In normal skin the epidermis is heavily innervated by nerve fibers immunoreactive for protein gene product (PGP) 9.5, whereas fibers immunoreactive for substance P (SP) and calcitonin gene-related peptide (CGRP) are typically associated with blood vessels. There was nearly complete degeneration of epidermal nerve fibers and the subepidermal neural plexus in capsaicin-treated skin, as indicated by the loss of immunoreactivity for PGP 9.5 and CGRP. The effect of capsaicin on dermal nerve fibers immunoreactive for SP was less obvious. Capsaicin decreased sensitivity to pain produced by sharp mechanical stimuli and nearly eliminated heat-evoked pain within the injected area. Limited reinnervation of the epidermis and partial return of sensation occurred 3 weeks after treatment; reinnervation of the epidermis was; 25% of normal, and sensation improved to 50–75% of normal [67-68].

2.18. Carum carvi

The analgesic effect of *Carum carvi* (100 and 500 mg/kg) was tested in acute and chronic pain in formalin test in mice. The results indicated that *Carum carvi* has analgesic effect in both doses in acute and chronic phases and the higher dose of the drug was more effective ($P<0.01$) [69].

2.19. Cassia occidentalis

The ethanol and water extracts of *Cassia occidentalis* leaves were screened for antinociceptive activity using acetic acid induced writhing test, hot plate test and tail immersion test in mice. The antipyretic potential of the extract was evaluated using yeast induced pyrexia method in rats. The results showed that ethanol and water extracts had significant ($P<0.01$) dose dependent antinociceptive and antipyretic properties at a dose of 150 and 300 mg/kg. The inhibition produced by the highest dose (300 mg/kg) of the extracts was significantly ($P<0.01$) lower than that by acetylsalicylic acid (100 mg/kg). Both the ethanolic and water extracts of *Cassia occidentalis* showed significant ($P< 0.01$) effect on pyrexia induced by yeast [70-71].

2.20. Citrullus colocynthis

The analgesic activities of Tunisian *Citrullus colocynthis* immature fruit and seed organic extracts (petroleum ether, chloroform, ethyl acetate, acetone and methanol extract) were assessed by acetic acid writhing test in rats. All extracts

displayed an important analgesic activities at different doses (0.05 and 1 mg/kg for analgesic effect) without inducing any side effects [72-73].

2.21. Citrus medica

The analgesic activities of ethyl acetate extract of *Citrus medica* peel (EtCM) (200, 300 and 400 mg/kg) were studied in carrageenan induced inflammatory pain in rats. Anti-inflammatory activity was assessed by measuring paw volume in rats. Analgesic activity was evaluated for its central and peripheral actions by using hot plate, plantar, pin prick and mechanical allodynia tests in rats. The extract (400 mg/kg) produced significant analgesic and anti-inflammatory effects [74].

The analgesic effect of fresh decoction of Citrus *medica* fruits was studied in rats. The decoction was prepared from fresh fruits in distilled water and the volume was reduced to $1/4^{th}$. Three doses of decoction (1, 2 and 4ml/kg, po) were tested for analgesic activity using tail immersion method and hot plate method. Diclofenac sodium (10mg/kg, ip) was used as standard. The decoction at doses (2 and 4ml/kg) showed significant increase in latency to flick compared to control in tail immersion method. Whereas the decoction of *Citrus medica* at all three doses showed significant increase in the mean basal reaction time in hot plate method. In both methods, analgesic effect of 4ml/kg decoction was observed comparable to the standard drug [75-76].

2.22. Clerodendrum inerme

Clerodendrum inerme were investigated for analgesic effects at the dose 125-400 mg/kg using acetic acid induced writhing methods. The extract produced significant analgesic activity. However, the inhibitory effect of diclofenac sodium (10 mg/kg) on acetic acid induced writhing was greater than methanol extract (500 mg/kg However, the inhibitory effect of diclofenac sodium (10 mg/kg) on acetic acid induced writhing was greater than methanol extract (500 mg/kg [77-79].

The analgesic, and antipyretic effects of aqueous extract obtained from *Clerodendrum inerme* leaves (AECI) was investigated in rats and rabbits. Analgesic effect of AECI was evaluated by Hot plate, Tail Flick and Tail immersion methods in albino rats. Antipyretic activity of AECI was evaluated by milk-induced hyperpyrexia in rabbits. The AECI produced significant ($P<0.001$) analgesic activity in all models. Furthermore, the AECI potentiated the Diclofenac sodium-induced analgesic effect in albino rats. Treatment with AECI showed a significant ($P<0.001$) dose-dependent reduction of pyrexia in rabbits [80].

2.23. Clitoria ternatea

The analgesic activity of *Clitoria ternatea* flower extract was studied in mice (hot plate). The petroleum ether (60-80 ◦ C) extract possessed significant analgesic properties [81-82]. The analgesic activities of the methanolic extract of *Clitoria ternatea* Linn. leaves were examined at the doses of 200 and 400 mg/kg on mice. The analgesic activities were investigated using acetic acid induced writhing test. The plant extract's Central Nervous System (CNS) depressant activity was evaluated by using hole cross and open field tests. Acetic acid induced writhing test revealed that the extract at the lower dose inhibited 82.67% and at the higher dose produced a maximum of 87.87% inhibition of writhing that is comparable to the reference drug, diclofenac sodium. The results of CNS depressant activity showed that the extract decreased the dose dependent motor activity and exploratory behavior of mice in hole cross and open field test. The number of field crossed in open field test and hole crossed in hole cross test decreased as time approached [83]. On the other hand, the possible mechanism underlying the antinociceptive action of methanolic extracts of *Clitoria ternatea* leaf and root was studied using several antinociception models. The different antinociception models such as hot plate, tail-flick and formalin tests were used along with naloxone (a non-selective opioid antagonist) to establish the antinociceptive activity of both leaf and root extracts. Both *Clitoria ternatea* leaf and root extracts markedly demonstrated antinociceptive action in experimental animals. Results of formalin test showed that the antinociceptive activity of the extracts may be mediated at both central and peripheral level. Moreover, the results of hot plate and tail-flick tests further confirmed that *Clitoria ternatea* root extract mediated antinociceptive activity centrally at supraspinal and spinal levels whereas, the *Clitoria ternatea* leaf extract's antinociceptive activity is mediated centrally at supraspinal level only. The authors believe that the opioid receptors are probably involved in antinociceptive activity of both *Clitoria ternatea* root extract [84].

2.24. Conium maculatum

Alkaloidal fraction of *Conium maculatum* aerial parts exhibited significant analgesic activity at a dose of 200 mg/kg as it showed significant increase in tail flicking reaction time with respect to the control, during 2 h intervals of observation [85-86]. Conmaculatin (2-Pentylpiperidine), a novel volatile alkaloid related to coniine identified from *Conium*

maculatum showed strong peripheral and central antinociceptive activity in mice, which observed in a narrow dose range (10–20 mg/kg). It was found to be lethal in doses higher than 20 mg/kg [87].

2.25. Cordia myxa

The analgesic effect of the hydro-alcoholic extract of fruit of *Cordia myxa* was investigated in mice by using formalin test and acetic acid tests. Normal saline, oral indomethacin, intraperitoneal tramadol, 100 mg/ kg, oral hydro-alcoholic extract of fruit of *Cordia myxa*, 200 mg/ kg orally and 100 mg/ kg intraperitoneally were used for comparison. The duration of foot lickings were calculated in formalin- administered within 0 to 5 min (acute phase) and 15 to 25 (chronic phase). Acetic acid-induced writhings were counted within 10 min. The results showed that hydro-alcoholic extract of *Cordia myxa* fruit possessed analgesic and properties in both acute and chronic phases [88-89].

The analgesic activity of different extracts of several species of Cordia was evaluated in rat. The results obtained showed that the petroleum ether and alcoholic extracts of *Cordia myxa* leaves exerted the most significant analgesic activity [90-92].

The ability of *Cordia myxa* extract in potentiating the analgesic effect of mefenamic acid (ponstan) was investigated in mice. Two tests were employed, hot plate test and formalin test. Mefenamic acid and *Cordia myxa* extract were given (each one alone) orally as aqueous solutions at a dose of 100mg and 600mg per kg. *Cordia myxa* extract alone increased the reactive time to the thermal stimuli. Simultaneous gavages of half of above mentioned doses of *Cordia myxa* extract and mefenamic acid (ponstan) had significantly prolonged the reactive time to the thermal stimulus. This could be due to a synergistic action through a common mechanism of *Cordia myxa* extract and ponstan in producing analgesia and relieving pain by disrupting the chain of synthesis of prostaglandin. In formalin test, a combination of *Cordia myxa* extract at a dose of 300mg/kg and mefenamic acid (ponstan) at a dose of 50 mg per kg was given before the injection of diluted formalin solution, they were significantly showed antinociceptive effect at the early and late phases, which could be attributed to their inhibitory effect on the nociceptive system and inflammatory mediators [93].

2.26. Coriandrum sativum

The analgesic effects of *Coriandrum sativum* seeds were evaluated in animal model, writhing and formalin tests. In writhing test, only the essential oil (4ml/100g, po) had a significant analgesic effect ($P<0.01$). However, the total extract, polyphenolic extract and essential oil of coriander, had significant effect in both phases of formalin test [94-95]. The analgesic effects of the extract were assessed using hot plate method. Aqueous extract at 50, 100 and 200 mg/kg significantly produce analgesic activity compared to control group [96].

The role of opiate system in the antinociceptive effects of *Coriandrum sativum* (CS) was studied in acute and chronic pain in mice using hot plate (HP), tail flick (TF) and formalin (FT) tests, and its effects were compared with dexamethasone (DEX) and stress (ST). CS (125 250, 500 and 1000 mg/kg, ip), DEX (0.5, 1 and 2 mg/kg, ip), vehicle (VEH) or swim stress were used 30 min before the pain evaluation tests. Acute and chronic pain was assessed by HP, TF and FT models. In addition, Naloxone (NAL, 2 mg/kg, ip) was injected 15 min before the CS extract administration in order to assess the role of opiate system in the antinociception of CS. Results indicated that CS, DEX and ST have analgesic effects ($P<0.01$) in comparison with the control group and higher dose of CS was more effective ($P<0.001$). Pretreatment with NAL modulated the antinociceptive effects of CS in all models ($P<0.001$). The findings showed an interaction between antinociceptive effects of CS and opiate system [97].

2.27. Cressa cretica

The analgesic and antipyretic activities of methanolic extract of *Cressa cretica* at different doses (100, 150 and 200 mg/kg) was studied using hot plate, acetic acid induced writhing and yeast induced hyperthermia methods. Methanolic extract of *Cressa cretica* showed significant analgesic and antipyretic activities at the dose of 200 mg/kg in all models studied [98-99].

2.28. Cuminum cyminum

Acetic-acid induced writhing and hot plate, were used for evaluation of analgesic effects of *Cuminum cyminum* extracts (200 and 500 mg/kg for aqueous and ethanolic extract). Both the aqueous and ethanolic extracts showed highly significant analgesic activity in acetic-acid induced writhing, while only the ethanolic extracts were effective in hot plate method [100-101].

The potential anti-nociceptive activities of the fruit essential oil of *Cuminum cyminum* has been evaluated in chemical (formalin test) and thermal (tail-flick test) models. The essential oil at the doses ranging between 0.0125 and 0.20 ml/kg

exhibited a significant and dose-dependent analgesic effect in both model. Moreover, the essential oil had no analgesic effect in tail flick test as a model of acute pain [102].

2.29. Cynodon dactylon

The analgesic and anti-pyretic activities of aqueous extract of *Cynodon dactylon* at different doses was studied using hot plate, acetic acid induced writhing and yeast induced hyperthermia in rats. *Cynodon dactylon* showed significant analgesic and anti-pyretic activities in all models studied. At the dose of 600 mg/kg, the aqueous extract possessed significant decrease in rectal temperature of mice similar to that shown by paracetamol [103-105].

2.30. Cyperus rotundus

The analgesic effects of *Cyperus rotundus* essential oils were evaluated using formalin induced writhing model in rats. The analgesic effects was evaluated on both first (0–5 min) and second (15-30 min) phases of formalin induced pain. The phases corresponded to neurogenic and inflammatory pains, respectively. Essential oil inhibited both, neurogenic and inflammatory pain ($P< 0.01$) at dose of 500mg/kg, whereas lower doses of essential oil significantly $P<0.05$ blocked the inflammatory pain [106-107].

Aqueous, ethyl acetate, methanol and TOF-enriched extracts of *Cyperus rotundus* (300, 150, and 50 µg/ml) were evaluated for their analgesic activities in mice. The tested extracts were able to reduced the number of abdominal contractions caused by acetic acid, revealing the peripheral analgesic activity of these extracts. No toxicity was recorded in mice treated with doses up to 300 mg/kg[108].

Tail flick method was used for the determination of analgesic activity. The temperature and duration were 51 ± 1C° and 0, 1, 2, 3 and 4 hours respectively. *Cyperus routunds* ethanolic extract 300 and 500mg/kg orally showed significant analgesic activity [109].

The ethanol extract of *Cyperus rotundus* showed significant analgesic properties as evidenced by the significant reduction in the number of writhes and stretches induced in mice by 1.2% acetic acid solution. It also potentiated analgesia induced by morphine and pethidine in mice [110].

The antinociceptive activity of the extract of whole plant of *Cyperus rotundus* was investigated in thermal-induced (hot plate and tail immersion) and chemical-induced (formalin) nociception models in mice at three different doses (50, 100 and 200 mg/kg; po). Morphine sulphate (5 mg/kg, ip.) and diclofenac sodium (10 mg/kg, ip) were used as reference analgesic agents. In the hot-plate and tail-immersion tests, the extract significantly increased the latency period to the thermal stimuli at all the tested doses (50, 100 and 200 mg/kg) ($P<0.05$). The significant increase in latency was clear from the observations at 60 and 90 min. In formalin-induced paw licking test oral administration of extract of whole plant of *Cyperus rotundus* at 100 and 200 mg/kg doses decreased the licking of paw in early phase. All the tested doses (50, 100 and 200 mg/kg) significantly decreased the licking of paw in late phase of the test ($P< 0.001$). The dose 200 mg/kg was most effective showing maximum percentage of inhibition of licking in both early (61.60%) and late phase (87.41%) [111].

The effect of *Cyperus rotundus* extract and its constituents was studied on the transient receptor potential vanilloid 1 channel (which was a nonselective cation channel that senses various noxious chemical and thermal stimuli, and involves in heat- and UV-induced skin aging). Ethylacetate and hexane fractions of the methanol extract were found to partially inhibit transient receptor potential vanilloid 1 channel activity, and at a concentration of 90 µM, oleanolic acid, which was one of three constituents isolated from the ethylacetate fraction, inhibited this activity by 61.4 ± 8.0%. The results highlight the potential therapeutic effects of *Cyperus rotundus* in the contexts of analgesia and UV-induced photo-aging [112].

The alcoholic extract of *Cyperus rotundus* showed significant ($P<0.001$) antipyretic activity against pyrexia induced in rats by the subcutaneous injection of suspension of dried Brewer's yeast in gum acacia in normal saline [113].

The alcoholic extract of *Cyperus rotundus* showed highly significant ($P<0.001$) antipyretic activity against pyrexia produced in albino rats by the subcutaneous injection of suspension of dried Brewer's yeast. However, a specific fraction obtained from the petroleum ether extract showed significant anti-pyretic effect similar to acetyl salicylic acid. The petroleum ether extract and essential oil of *Cyperus rotundus* possessed analgesic activity [114-115].

2.31. Dalbergia sissoo

The analgesic properties of the methanolic extract of leaves of *Dalbergia sissoo* were evaluated by using acetic acid induced writhing and hot plate tests in mice. Oral pretreatment with the leaves extracts of *Dalbergia sissoo* significantly decreased the writhing movements in mice in acetic acid-induced writhing test and significantly increase the mean pain latency time in mice placed on the hot plate at 50°C at dose dependant manner[116].

The alcoholic extract of *Dalbergia sissoo* seeds was evaluated for analgesic and antipyretic activities. The peripheral analgesic activity of seed extract (SSE) was studied using acetic acid-induced writhing in mice and by Randall-Selitto assay in rats. Furthermore, the central analgesic activity of SSE was studied by tail-clip test and hot plate method in mice. The antipyretic activity of SSE was studied in Brewer's yeast-induced pyrexia in rats. The alcoholic extract of *Dalbergia sissoo* seeds was significantly decreased writhing movements in mice by acetic acid-induced writhing test and significant increased in the pain threshold capacity in rats in Randall-Selitto assay and the reaction time in hot-plate test but not in tail-clip test. Moreover, it also showed significant antipyretic activity in Brewer's yeast-induced pyrexia in rats throughout the observation period of 6 h[117].

The analgesic activity of the ethanol extract of the bark of *Dalbergia sissoo* was investigated using the tail flick method in Wistar rats. The extract at the doses of 300, 500 and 1000 mg/kg was reported to possess significant and dose dependent, central analgesic activity, compared with the standard drug aspirin at the dose of 300 mg/kg. An ethanol extract of the leaves of *Dalbergia sissoo* showed both peripheral and central analgesic activity in a dose dependent manner. Peripheral analgesic activity was studied using the acetic acid-induced writhing reflex and Randall-Selitto assays in mice as well as central analgesic activity was studied using the hot-plate and tail-clip tests in mice. In writhing test, the extract (100, 300 and 1000 mg/kg) moderately inhibited writhing in mice while aspirin (300 mg/kg) showed strong activity; in Randall-Selitto assay, the extract failed to increase pain threshold level at the doses of 100 and 300 mg/kg but exhibited significant ($P<0.01$) activity at the dose of 1000 mg/kg and comapared with the aspirin (300 mg/kg) which increased pain threshold throughout the observation period of 1 to 3 h; in hotplate test, the extract (1000 mg/kg) increased reaction time at 2 and 3 h while pathidine (5mg/kg) increased reaction time at 1 and 2 h; in tail-clip test, the extract failed to increase reaction time even at the higher dose of 1000 mg/kg.

The ethanol extract of the leaves of *Dalbergia sissoo* showed significant antipyretic activity in a Brewer's yeast-induced pyrexia assay in rats. The extract at the doses of 100 and 300 mg/kg showed significant antipyretic activity at 1 h after drug administration while at the 1000 mg/kg showed activity throughout the observation period up to 6 h and results were highly comparable with aspirin (300 mg/kg)[118-120].

The analgesic potential of the ethanolic bark extract of *Dalbergia sissoo* bark was measured by the Radiant Heat method (tail flick method). The bark extract showed significant analgesic activity as evidenced by the increase in reaction time to the pain stimulus. The extract 300 mg/ kg and 500 mg/kg failed to alter pain threshold capacity but increased significantly at the dose of 1000 mg/kg at 30 min[121].

The antinociceptive activity of ethanolic extract of the plant bark of *Dalbergia sissoo* (Roxb.) was investigated using tail flick method on Wistar rats. Three different dose levels (300, 500, and 1000 mg/kg) in 0.5% carboxyl methyl cellulose (CMC) were administered orally. At these doses, the extract exhibited significant and dose-dependent antinociceptive activity[122].

2.32. Daphne mucronata

The analgesic effects of ethyl acetate extract of aerial parts of *Daphne mucronata* and the possible involvement of opioid receptors were studied in mice using formalin test. Single doses of 2.5, 5.0 and 10.0 mg/kg of ethyl acetate extract of *Daphne mucronata* were intraperitoneally administered to the mice 30 min before carrying out the analgesic test. The results revealed that the extract (2.5, 5.0 and 10.0 mg/kg) increased the pain threshold of mice and induced analgesia in both phases of formalin test. Like morphine sulfate (5.0 mg/kg, ip), the extract also showed more effective analgesic effect on the late phase of formalin test. Pre-treatment of animals with naloxone (5.0 mg/kg ip) did not inhibit the effects of the extract[123-124].

2.33. Datisca cannabina

Ethanolic (50%) extract of seeds and flowers exhibited marked sedative, mild analgesic and antipyretic activity in rats[125].

2.34. Datura fastuosa

The aqueous extracts of *Datura fastuosa* leaves and seeds were evaluated for the analgesic effect on acetic acid-induced writhing and hot plate reaction in mice. The results revealed that *Datura fastuosa* leaves and seeds extracts at doses of 400 and 800 mg/kg orally induced analgesic effects. The analgesic activity of leaf extract is reduced by naloxone but not that of seed extract[126-127].

2.35. Datura stramonium

The analgesic effect of alcoholic *Datura stramonium* seed extract was evaluated in acute and chronic pain using hot plate and formalin tests. The extract when intraperitonealy administered to the animals, they alleviated the pain dose dependently, and ED_{50} was equal to 25 and 50 mg/kg in hot plate and formalin tests, respectively[128].

2.36. Daucus carota

The ethanolic extract of *Daucus carota* seeds was investigated for analgesic activity at the doses of 100, 200 and 400 mg/kg, orally. The acetic acid-induced writhing response and formalin-induced paw licking time in the early and late phases of mice were used to assess analgesic activity. *Daucus carota* seeds extract (200 and 400 mg/kg, po) significantly attenuated the writhing responses induced by an intraperitoneal injection of acetic acid and late phase of pain response induced by an subplantar injection of formalin in mice[129].

Daucus carota seed extracts were investigated as cyclooxygenase (COX) enzymes inhibitor. Compounds, 2,4,5-trimethoxybenzaldehyde, oleic acid, trans-asarone and geraniol were isolated from seed extract. They showed 3.32, 45.32, 46.15, and 3.15% of prostaglandin H endoperoxide synthase-I (COX-I) inhibitory activity and 52.69, 68.41, 64.39 and 0% prostaglandin H endoperoxide synthase-II (COX-II) inhibitory activity, respectively at 100 mg/ml. Compound 2,4,5-trimethoxy benzaldehyde showed selectivity towards COX-II enzyme inhibition at 100 µg/ml. The COX-II/COX-I ratio for this compound was 17.68 at 100 µg/ml compared to solvent control[130-131].

2.37. Desmostachya bipinnata

The tail immersion method was used to investigate the analgesic activity of petroleum ether, benzene, chloroform, ethanol and aqueous extract of the whole parts of *Desmostachya bipinnata*. Almost all the extracts possess a significant analgesic effect ($P<0.05$)[132]. The hydro-alcoholic extracts of *Desmostachya bipinnata* roots were investigated for analgesic potential (hot plate method) on experimental model. The analgesic effect of the extract (300 mg/kg) was comparable to that produced by 150 mg/kg of analgin[133-134].

2.38. Erodium cicutarium

A 70% ethyl alcohol thick extract from equal amounts of the aerial parts of *Geranium sanguineum*, *Astragalus glycyphyllos*, *Erodium cicutarium* and *Vincetoxicum officinalis* was prepared to study of its analgesic effects. The analgesic effect was determined by hot/ cold plate and Randall & Selitto test (Analgesy-meter). The extract showed no reliable analgesic effect (excluding the dose of 1g/kg, 1st hour, $p = 0.031$). However, a reliable analgesic effect was recorded with the using of 2 g/kg of the extract on the 2nd and 3rd hour ($P = 0.037$, $p = 0.022$). In repeated dose of the extract, the treated animals showed statistically reliable analgesic effect at the dose of 1g/kg, on the 1st, 2nd and 3rd hour ($P = 0.024$, $p = 0.029$, $p = 0.021$)[135-136].

2.39. **Echium italicum**

The analgesic effect of the ethanol extracts from the roots and herbs of *Echium italicum* was investigated in mice using acetic acid-induced writhing and tail flick methods. The analgesic effect of root extracts of *Echium italicum* (0.5 mg/g) was comparable with the standard drugs, Aspirin and Morphine. The findings imply the involvement of both peripheral and central antinociceptive mechanisms[137-138].

2.40. Equisetum arvense

The antinociceptive effects of hydroalcoholic extract of stem from *Equisetum arvense* were studied in mice. The extract 10, 25, 50 and 100mg/kg, ip, reduced the writhing induced by acetic acid 49, 57, 93 and 98%, respectively. In the formalin test, 50 and 100mg/kg, ip, reduced 80 and 95% the licking activity in the first phase, but in the second phase only the latter dose diminished the licking time (35%). In both phases, naloxone failed to revert the analgesic effect of the extract. In the hot-plate test, the extract at 100 and 200mg/kg does not change the latency to licking or jumping[139-140].

2.41. Eryngium creticum

Ethanolic and aqueous extracts obtained from either aerial parts or roots of eight *Eryngium* species growing in Turkey, were evaluated for their *in vivo* antinociceptive activities, using p-benzoquinone-induced writhing test. Ethanolic extracts either from the aerial parts or roots showed apparent antinociceptive activity[141-142].

2.42. Eucalyptus camaldulentis

1,8-cineole (cineole) and beta-pinene, two monoterpenes isolated from the essential oil obtained from *Eucalyptus camaldulensis* leaves were tested for antinociceptive properties. Tail-flick and hot-plate methods, reflecting the spinal and supraspinal levels, respectively, were used in mice and/or rats using morphine and naloxone for comparison. Cineole exhibited an antinociceptive activity comparable to that of morphine, in both algesic stimuli. A significant synergism between cineole and morphine was observed, but naloxone failed to antagonize the effect of cineole. Beta-pinene exerted supraspinal antinociceptive actions in rats only and it reversed the antinociceptive effect of morphine in a degree equivalent to naloxone, probably acting as a partial agonist through the mu opioid receptors[143-144]. *Eucalyptus camaldulentis* possessed an anti-nociceptive effect against both acetic acid-induced writhing and hot plate-induced thermal stimulation in mice[145].

2.43. Foeniculum vulgare

The analgesic action of the ethanolic extracts *Foeniculum vulgare* (50,100 and 200mg/kg, ip) was studied in Wistar rats and Swiss Albino mice. Analgesia was studied in albino rats using formalin test and in albino mice using writhing test. The ethanolic extract produced significant ($P<0.001$) dose-dependent inhibition of pain response elicited by acetic acid and formalin tests [146].

The effects of *Foeniculum vulgare* extract in reduction of pain and other systemic symptoms accompanying primary dysmenorrhea were studied using double-blind clinical trial carried out on female students [90 (46 cases and 44 controls)] at Shahid Beheshti University, Iran. Five capsules containing 46 mg of *Foeniculum vulgare* and identical placebos were provided to be taken daily by the case and control groups respectively, during the first three days following the onset of dysmenorrheal pain whenever they needed the medications. The severity of pain in the treated group with *Foeniculum vulgare* extract, showed a significant difference ($P<0.001$) in comparison with the placebo group, in addition to significant differences in systemic symptoms [147]. The antinociceptive activities of some components of *Foeniculum vulgare* (alpha-pinene, limonene, fenchone, trans-anethol and alpha-copaene) were investigated for analgesic effects in mice using tail-flick tests. The drugs were injected intraperitoneally in doses of 0.05, 0.1 and 0.2 ml/kg. Alpha-pinene and fenchone caused significant reduction in the nociceptive threshold in the tail-flick test, while, other tested compounds showed no significant analgesic effects[148].

The methanolic extract of the aerial parts of *Foeniculum vulgare* subsp. *piperitum* exhibited the highest antinociceptive activity at a dose level of 2000 mg/kg, while the activity exhibited by the ethyl acetate extract was at (800 mg/kg). On the other hand, *n*-hexane extract (700 mg/kg) and methylene chloride extract (500 mg/kg) exhibited similar antinociceptive activities, being less than that of acetylsalicylic acid (200 mg/kg)[149].

Crude ethanolic extracts of *Foeniculum vulgare* seeds was investigated for antinociceptive activity. Results showed that the dosage of 298 mg/kg, compared to the indomethacin pattern, led to a significant reduction in the number of abdominal writhings in the animals[150].

The hot plate method was used to determine the analgesic activity of the plant . *Foeniculum vulgare* ethanolic fruit extract (500 mg/kg, orally) showed a moderate analgesic activity that was significant after 90 ($P<0.5$) and 150 ($P<0.0l$) min of its administration. The observed analgesia was of higher magnitude at 150min than after 90min. The ethanolic fruit extract similarly showed an antipyretic activity that was evident at 30 and 90 rnin ($P<0.0l$) but not at 150min[151].

2.44. Fumaria officinalis

The analgesic effects of ethanol extract of arial parts of *Fumaria officinalis* were investigated using different models. The result of the effect of *Fumaria officinalis* extract on hot plate induced pain in mice showed that the extract 200 and 500 mg/kg significantly ($P<0.001$ and $P<0.0001$ respectively) increased the post drug PRT. The tail withdrawal response or tail flick time was significantly ($P<0.0001$) increased from 3.583±0.2386 seconds in the control group (10ml/ kg normal saline) to 13.75±0.2141seconds in the diclofenac sodium 10 mg/ kg and 12.42±0.2386 seconds in the highest dose of the extract (500 mg/kg). The percentage inhibition of writhing was also dose dependently increased from zero in the control group (normal saline) to 33% in the group that received 500mg/ kg of the extract. In acetic acid induced writhing

method, there was significant analgesic effects produced by were given 200mg/ kg and those treated with the reference drug diclofenac 500 mg/ kg of extract[152-153].

2.45. Fumaria parviflora

The antipyretic activity of *Fumaria parviflora* was studied in rabbits. Pyresis was induced by subcutaneous yeast injections. Significant oral antipyretic activity in rabbits was exhibited by hexane-, chloroform- and water-soluble extracts of *Fumaria parviflora* comparable with aspirin. The antipyretic activity was more prominent in the hexane-soluble extract [154-155].

The antinociceptive effects of the methanolic extract of *Fumaria parviflora* were evaluated in mice subjected to acute thermal [hot-plate] and persistent chemical [formalin] pain stimuli. Intra-peritoneal injection of the percolated extract evoked significant antinociceptive effects at a dose of 100 mg/kg in the second phase of formalin test. The maximum antinociceptive effect was induced by the dose of 300 mg/kg that was significant in both phases of formalin test. The results showed that only percolated extract had significant antinociceptive effect in hot-plate. Pretreatment of mice with naloxane, an opioid antagonist did not change antinociceptive effect of percolated extract in formalin test, but in hot-plate it increased extract's effect after the first 15 minutes [156].

2.46. Geum urbanum

In a screening of Swedish traditional remedies *Calluna vulgaris* and *Geum urbanum* were reported to inhibit prostaglandin biosynthesis and platelet activating factor (PAF)-induced exocytosis *in vitro*[157].

2.47. Hedera helix

The methanolic extract of the whole plant was partitioned with hexane, chloroform and ethyl acetate. The analgesic activity of the crude extract and subsequent solvent fractions of *Hedera helix* was carried in NMRI mice. In acetic acid induced writhing test, the crude extract provoked 33.33 and 55.90% pain reduction at 50 and 100 mg/kg ip respectively. When fractionated, the hexane fraction of plant did not produce significant reversal of induced pain. The chloroform fraction of the plant exhibited prominent pain inhibition: 48.71 and 65.70% at 50 and 100 mg/kg ip respectively. For ethyl acetate fraction, significant activity was observed with 40.76 and 59.76% at 50 and 100 mg/kg ip respectively, while, aqueous fraction elicited most profound effect 50.77 and 70.71% blockade of noxious stimulation at 50 and 100 mg/kg ip respectively[158].

2.48. Helianthus annuus

The analgesic effects of the ethanol extract of leaves of *Helianthus annus* (0.5 g/kg, 2 g/kg and 4 g/k) were investigated in rats. Treatment with the extract was significantly increased the mean tolerance time of rats to thermal noxious stimuli compared to control animals and appeared to be more effective than 10 mg/kg of indomethacin treatment[159-160]. The methanol extract of seeds of *Helianthus annuus* was evaluated for analgesic activity using acetic acid induced writhing and hot plate methods In acetic acid-induced writhing test, the extract showed significant ($P<0.05$) analgesic potential at doses of 100 and 200 mg/kg (50.35 and 57.85% inhibition, respectively). In the hot plate method, increase ($P<0.05$) of latency period was also observed in comparison to standard aspirin. At 60 minutes, the latency period of two different doses (100 and 200 mg/kg) was found at 13 ± 0.91 and 16.5 ± 1.55 second[161].

2.49. *Hibiscus rosa-sinensis*

The methanolic extract of *Hibiscus rosa- sinensis* leaves (250 and 500 mg/kg, orally) was studied for anti-nociceptive (acetic acid-induced writhing response and tail flick method). The methanolic extract possessed significant dose-dependent analgesic activity[162].

The antipyretic activity of the root extract of *Hibiscus rosa sinesis*, was evaluated in yeast induced pyrexia and the analgesic potentials was investigated in tail flicking method in rats at a dose of 250mg/kg. The aqueous root extract showed significant antipyretic and analgesic activities[163]. The anti-pyretic activity of *Hibiscus rosa-sinensis* aqueous extracts was evaluated in fever induced by yeast suspension (intraperitoneally 0.1 g/kg in mice. The animals with fever were administered orally with aqueous extracts of *Hibiscus rosa-sinensis* (500 mg/kg). The result of the study showed that *Hibiscus rosa-sinensis* aqueous extracts significantly ($P<0.05$) effective in combating fever[164].

2.50. Hibiscus sabdariffa

The effects of the extracts from *Hibiscus sabdariffa* calyces on nociceptive response were studied using writhing, hot plate and formalin test in mice and the antipyretic activity by using yeast-induced fever in rats. Oral administration of the ethanol extract at the dose of 800 mg/kg significantly decreased the number of contortions and stretchings induced by acetic acid in mice. Neither the ethanol nor aqueous extract had an effect in the formalin and hot plate tests in mice. The ethanol and the vacuum dried extract of *Hibiscus sabdariffa* calyces (200-800 mg/kg, po) decreased the yeast-induced fever in rats165].

The antinociceptive effects of the ethanolic calyx extract of *Hibiscus* sabdariffa were studied in mice. The antinociceptive activity of the extract was evaluated by using the acetic acid-induced writhing test. The extract inhibited writhing in mice significantly compared with control ($P<0.01$)[166].

The aqueous extracts of *Hibiscus sabdariffa* were tested for analgesic and antipyretic activities in animal models. The extract had an inhibitory effect on yeast induced pyrexia and showed significant effect on the hot plate reaction time[167].

2.51. Hyoscyamus Species

The analgesic (acetic acid induced writhing response and the other formalin-induced paw licking in rats) and anti-pyretic properties (brewer's yeast induced fever in rats) of standardized *Hyoscyamus albus* methanolic extract were investigated experimentally. 100 and 200 mg/kg of *Hyoscyamus albus* methanolic extract decreased the acetic acid induced writhing responses and the licking time in the second phase of the formalin test. Moreover, it showed dose-dependent lowering of the body temperature up to 3h at both doses the effect was comparable to that of paracetamol[168-169].

The methanolic extract of seeds of *Hyoscyamus niger* was evaluated for analgesic, and antipyretic activities in experimental animal models at different doses. The methanolic extract of seeds of *Hyoscyamus niger* produced significant increase in hot plate reaction time, while decreasing writhing response in a dose-dependent manner indicating analgesic activity. It also exhibited antipyretic activity in yeast-induced pyrexia model[170].

The analgesic effect of *Hyoscyamus niger* seeds alcoholic extract (500, 1000 and 2000 mg/kg, ip) was studied in acute and chronic pain in rats. The results revealed that injection of *Hyoscyamus niger* seeds alcoholic extract reduced the acute and chronic pain induced by formalin significantly ($P<0.001$) and significantly increased chronic pain threshold[171].

The antinociceptive effect of the metanolic extract of *Hyoscyamus reticulatus* was investigated in mice. Two models were used to study the effects of the extracts on nociception, acetic acid-induced writhing test and hot plate test in mice. The methanolic extract (50 mg/kg) possessed significant ($P<0.05$) analgesic activity comparable with diclophenac sodium, evidenced by increase in the reaction time by hot plate method and significant ($P<0.05$) reduction in acetic acid - induced writhings in mice with a maximum effect of 35.56 % reduction[172].

2.52. Hypericum triquetrifolium

The antinociceptive activity of *Hypericum triquetrifolium* lyophilized extract was investigated in mice. Formalin paw test and tail flick tests were used for the evaluation of the antinociceptive activity. The extract caused a significant dose-related inhibition of the first phase (50, 60 mg/kg, ip) and second phase (10, 25, 50 and 60 mg/kg, ip) of formalin induced hindpaw licking. Additionally, the extract administration (50, 60 mg/kg, ip) increased the tail flick latencies. No significant change was observed in any of the treatment groups in the sensorimotor performance test[173-174].

2.53. Inula graveolens

The antipyretic activities of the methanolic extract of *Inula graveolense* were examined in rats. The methanolic extract (400 mg/kg) showed a significant ($P<0.01$) dose dependent anti- pyretic effect in yeast induced elevation of body temperature. A dose-dependent analgesic action was obtained against chemical (writhing test) and thermal (hot-plate test) stimuli [175-176].

2.54. Jasminum sambac

The methanol extract (400 mg/kg) of *Jasminum sambac* flowers was investigated for analgesic activities using hot plate and acetic acid induced writhing models in animals. In the acetic acid-induced writhing model, the extract possessed

significant analgesic effects compared to the control, These effects were comparable to that induced by diclofenac sodium[177].

The analgesic activity of methanolic extract of root of *Jasminum sambac* (200 and 400 mg/kg) was evaluated in Wister albino rats and mice of using tail flick and acetic acid induced writhing method respectively. The results showed that the methanolic extract of Jasmine root possessed significant analgesic activity by both models, with a maximum effect for 400 mg/kg. The authors suggested central as well as peripheral mechanism of analgesic action[178].

The ethanol extract of the dried leaves of *Jasminum sambac* produced significant ($P<0.001$) writhing inhibition in acetic acid-induced writhing in mice at an oral dose of 250 and 500 mg/kg comparable to the standard drug diclofenac sodium at the dose of 25 mg/kg [179-180].

2.55. Juglans regia

The nociceptive effect of alcohol extract of *Juglans regia* leave (0.5, 1 and 1.5 mg/kg) alone and in combination with morphine was tested in rats. Alcohol extract of walnut leave in dose of 1.5 mg/kg caused a significant nociception decrease in acute phase of formalin test and this effect was dose dependent. Moreover, rats received a combination of morphine and alcohol extract showed more nociception especially in acute phase of formalin test, in comparison to the groups that received each separately [181].

2.56. Juniperus communis

Methanolic extract of *Juniperus communis* (100mg/kg and 200mg/kg) was tested for analgesic activity by different tests like formalin test, acetic acid induced writhing, and tail flick tests. The extract showed significant ($P< 0.01$) and dose dependent analgesic activity. The blocking effect of naloxone (2mg/kg ip) to the analgesic activity of the extract of *Juniperus communis* confirmed the central analgesic activity[182-183].

2.57. **Juniperus oxycedrus**

Methanol and dichloromethanol extracts of leaves and stems of *Juniperus oxycedrus* were tested for analgesic effects. The methanol extract exhibited an analgesic effect in models of chemical, mechanical and thermal stimulation whereas dichloromethanol extract showed only a significant effect in models of pain induced by chemical stimulation [184-185].

The antinociceptive activities of subextracts of *Juniperus oxycedrus* subsp. *oxycedrus* berries and leaves were evaluated using *p*-benzoquinone-induced writhing test in mice. The *n*-butanol subextract of *J. oxycedrus* subsp. *oxycedrus* berry ethanol extract exhibited significant antinociceptive activity without inducing any gastric damage or apparent acute toxicity[186].

2.58. Kochia scoparia (Bassia scoparia)

The 70% ethanol extract (KS-ext) from Kochiae Fructus at an oral administration of 500 mg/kg had an antinociceptive effect on writhing responses induced by acetic acid, but, it was ineffective in nociceptive response in the hot plate test. Oleanolic acid oligoglycoside, momordin Ic isolated from Kochiae Fructus significantly decreased the frequency of licking behavior within a unit of time at the late phase without affecting that of the early phase in the formalin test. KS-ext also inhibited the rise of vascular permeability induced by acetic acid, the increase of paw edema induced by carrageenin, histamine, serotonin or bradykinin and ear swelling induced by arachidonic acid. Momordin Ic also possessed an inhibitory effect on carrageenin-induced edema[187-188].

2.59. Lagerstroemia indica

The analgesic effect of water methanol *Lagerstroemia indica* leaves extract free from polysaccharide (extract A), and water methanol extract with polysaccharide (extract B), 100 mg /kg, was studied using an electric current as noxious stimulus applied to the rat's tail. Extract A of *Lagerstroemia indica* possesses higher analgesic activity and more potent than extract B, with 68% and 54% respectively of that of the standard dipyron-metamizole[189].

The antipyretic effect of water methanol *Lagerstroemia indica* leaves extract free from polysaccharide (extract A), and water methanol extract with polysaccharide (extract B), 100 mg/kg using intramuscular injection of 1 mg /100g of 44% yeast suspension in rats. Extract A of *Lagerstroemia indica* possessed antipyretic activity, it showed potency after one hour (65%) then it increased after two hours reaching 88%, while the potency of extract B was 35% after one hour then increased to 62% after two hours of treatment as compared to the reference drug, acetaminophen[190-191].

2.60. Lagerstroemia speciosa

The analgesic actions of an aqueous ethanolic extract of *Lagerstroemia speciosa* was investigated using formalin-induced pain, acetic acid-induced writhing and thermal (hot plate and tail immersion) tests in rats. The crude plant extract significantly increased the reaction time of hot plate and immersion tests. It decreased the writhings of acetic acid-induced abdominal contractions and lickings of formalin-induced pain. The results also showed that the aqueous ethanolic extract possessed both central and peripheral acting effects, this was confirmed by its effect on both phases of formalin-induced pain[192-193].

The analgesic potential of the flowers of *Lagerstroemia speciosa* extracts was assayed in mice, 16.68% inhibition of writhing was recorded for 400 mg/kg of the extract of Lagerstroemia speciosa. In central analgesic activity assay by tail-flick method, 48.24% elongation of the reaction time was observed after 30 min of administration of 400 mg/kg of the methanol extract of the flowers of *Lagerstroemia speciosa* [194].

The antinociceptive activity of chloroform extract of barks of *Lagerstroemia speciosa* was evaluated using an acetic acid-induced gastric pain model in mice. The chloroform extract of bark of *Lagerstroemia speciosa* exhibited significant inhibition of writhing (50.7%) at the highest dose tested (500 mg/kg). At the lower dose of 250 mg bark extract/kg, there was a decrease in the number of writhings compared to controls, but the decrease was not significant[195].

The ethanol extract of the dried fruits of *Lagerstroemia speciosa* was investigated for antinociceptive activities. The extract produced significant ($P<0.001$) writhing inhibition in acetic acid-induced writhing in mice at the oral dose of 250 and 500 mg/kg comparable to the standard drug diclofenac sodium at the dose of 25 mg/kg[196].

2.61. Lallemantia iberica

The antinociceptive effect of methanolic extract of (80, 100 and 300 mg/kg, ip) of *Lallemantia iberica* was evaluated in rats. *Lallemantia iberica* leaf extract significantly inhibited the number of contractions induced by acetic acid. All doses antinociceptive activity in the tail flick model. In formalin test, the highest effect was observed at dose of 300 mg/kg ($P<0.01$)[197-198].

2.62. Lantana camara

The antinociceptive activities of aqueous extract of *Lantana camara* (25, 50, 100 mg/kg) were studied using formalin pain test in rats. The administered doses showed significant ($P<0.05$) analgesic activity and minimal toxic effects[199].

Methanolic extracts of the leaves and bark of *Lantana* extract was screened for analgesic activity by acetic acid and hot plate. Methanolic leaf and bark extracts (100 mg/kg and 200 mg/kg) possessed analgesic activity[200].

The analgesic activity of petroleum ether, ethanol, acetone, methanol, hydro alcoholic and aqueous extracts (300mg/kg and 500mg/kg, orally) of the leaves of *Lantana camara* was studied using hot plate test in rats, the time for licking of the paws was recorded before, and 30 min after, the oral administration of the different extracts. The results showed that the latency time for licking was increased after treatment[201-202].

2.63. Lathyrus sativus

The analgesic activity was studied using acetic acid induced writhing and formalin induced paw licking methods in mice, while 2,4-dinitrophenol (DNP) induced pyrexia model was used to investigate the antipyretic activity in mice. The plant extracts significantly ($P<0.001$) inhibited the writhing induced by acetic acid in mice to 87.09% and 80.65% (200 and 300 mg/kg respectively) compared to the standard indomethacin (70.97%). The extracts (200 and 300 mg/kg respectively) also significantly ($P<0.001$) reduced the writhing to 43.39%, 64.15% in early and 46.15%, 97.44% in late phase of formalin-induced licking and biting. In 2,4-DNP induced pyrexia the extracts exhibited protection at 200 and 400 mg/kg, similar to standard drug aspirin at 150 mg/kg[203-204].

2.64. Lawsonia inermis

The analgesic effects of the mixture of *Lawsonia inermis* leaves with aqueous extract of *Ricinus communis* leaves was studied in rat osteoarthritis induced by intra-articular injection of mono sodium iodoacetate. Analysis of mechanical allodynia after 21 days, hotplate latency test after 10 days, spontaneous movements after 7 days, showed that the mixture possessed significant analgesic effects compared to the vehicle group[205-206].

The crude ethanolic extract of *Lawsonia inermis* (0.25-2.0 g/kg) produced significant and dose-dependent analgesic and antipyretic effects in rats. The butanol and chloroform fractions showed more potent analgesic and antipyretic effects than the crude extracts, the butanolic extract (500 mg/kg) was the most effective in the analgesic test. A pure compound was isolated from the chloroform extract (2-hydroxy-1,4-naphthaquinone, lawsone) which may responsible for these effects[207].

The analgesic activity of methanol , petroleum ether and ethyl acetate extracts of *Lawsonia inermis* leaves (250 and 500 mg/kg, ip) was evaluated by hot-plate and acetic acid induced writhing methods in mice. All the extract displayed significant analgesic effect (P<0.05-0.001) in acetic acid and heat induced pain models in a dose dependent manner[208].

The synergistic analgesic activities of chloroform extracts of leaves and roots tubers of *Lawsonia inermis* and *Chlorophytum borivilianum* was studied in mice by using tail immersion and hot plate methods. The results showed that the chloroform extract of both plants significantly produced analgesic activity at the dose level of 200 mg/kg, but combination of both the extract showed more analgesic activity as compare to each one[209-210].

The ethanol extract of the leaf of *Lawsonia inermis* was examined for analgesic properties using acetic acid induced writhing in mice. The ethanol extract at a dose of 500 mg/kg exhibited no significant (P<0.3) inhibition of writhing reflex (28.45 % inhibition) while the inhibition of diclofenac sodium was 82.7 % at a dose of 25 mg/kg[211].

2.65. Lepidium sativum

The antinociceptive effect of the aqueous extract of *Lepidium sativum* (20 mg/kg orally) was investigated, using acetic acid-induced writhing test and hot plate test in mice. The aqueous extract showed significant (P<0.05) analgesic activity evidenced by increase in the reaction time by hot plate method and significant (P<0.05) reduction in acetic acid - induced writhings in mice with a maximum effect of 27% reduction[212].

2.66. Linum usitatissimum

The analgesic (200 and 500 mg/kg extract) effects of *Linum usitatissimum* leaves extracts were evaluated in mice. Both doses showed analgesic activity, the 200 mg/kg possessed higher effects (P< 0.05)[213].

The methanol extract of *Linum usitatissimum* (300,500 and 1000 mg/kg) was studied for analgesic activity in mice by tail flick latency via the tail immersion method, in comparison with acetylsalicylic acid (300 mg/kg). The results showed that the methanolic extract possessed significant analgesic activity at doses of 300 and 500 mg/kg, but it was less potent than that of acetylsalicylic acid at 300 mg/kg. The most pronounced effect was produced by at a dose of 1000 mg/kg[214].

2.67. Luffa acutangula

The antinociceptive potential of the methanolic fruit extract of *Luffa acutangula* was evaluated in gastric pain model mice, where pain was induced through intraperitoneal administration of acetic acid, resulting in pain and concomitant abdominal constrictions. The extract at dose-dependently reduced the number of abdominal constrictions in mice caused by the gastric pain, by 46.7, 50.0, 53.3, and 63.3% at100, 200 and 400 mg/kg respectively. The results were statistically significant at all doses of the extract[215-216].

2.68. Luffa cylindrica

The peripheral analgesic activity aqueous and ethanol extracts of *Luffa cylindrica* was evaluated by acetic acid induced writhing method and the antipyretic activity was evaluated by Brewer's yeast induced pyrexia in rats. The aqueous and ethanol extracts showed significant analgesic activity and ethanolic extract 200 mg/kg was showed higher percentage of inhibition of wriths (72.56%) then the other doses. The aqueous and ethanol extracts also showed significant (P<0.05) antipyretic activity, compared to control group[217].

The analgesic activity of alcoholic and ethanolic extracts (100mg/kg) of *Luffa cylindrica* fruits was determined by acetic acid induced writhing in mice and tail immersion method in mice. Ethanolic extract showed significant analgesic activity by tail immersion method after 60 (P<0.01) and 90 minutes (P<0.001)[218].

Ethanol extracts (500 mg/kg, po) of leaves, male flowers and fruit peel of *Luffa cylindrica* were evaluated for analgesic effect using analgesy-meter test, a mechanically induced pain model. The tested extracts produced significant and

comparable analgesic effect as with diclofenac sodium. Analgesic response was continuously increasing till 3hrs[219-220].

2.69. Lycopus europaeus

The extract possessed highly significant (P<0.001) analgesic activity in a dose dependent manner on hot plate method, acetic acid induced writhing test and also on both the early and late phases of formalin test at the tested doses. In the hot plate method, the extract increased the reaction time of heat sensation to 60.81% and 66.52% at the doses of 250 and 500 mg/kg respectively. In acetic acid induced writhing test, the percent inhibition of writhing response by the extract was 62.87% and 70.66% at 250 and 500 mg/kg doses respectively (P<0.001). The extract also significantly inhibited the licking response at the dose of 500 mg/kg in both the early phase (55.11%, P<0.01) and the late phase (66.43%, P<0.01) of formalin test[221-222].

2.70. Lythrum salicaria

Different solvents extracts (petroleum ether, ethyl acetate, methanol, 50% aqueous methanol and aqueous extract) of the aerial parts of *Lythrum salicaria* were tested for anti-nociceptive activity using p-benzoquinone-induced abdominal constriction test in mice. Methanol extract was found to have inhibitory activity (P<0.05) at 100 and 200 mg/kg dose (26.9 and 30.1%, respectively). None of the extracts caused any gastric damage[223-224].

2.71. Mangifera indica

The analgesic effects of ethanol leave extract (2g/kg) of *Mangifera indica* were investigated experimentally by using acetic acid induced writhing response model. Oral administration of the ethanol leaves extract significantly (P<0.01) reduced the writhing response[225].

Vimang (20-1000 mg/kg, orally) dose-dependently inhibited the second phase of formalin-induced pain but not the first phase. The DE_{50} of the second phase was 8.4 mg/kg and the maximal inhibition was 99.5%. Vimang (20-1000 mg/kg, p.o.) significantly inhibited oedema formation (P<0.01 or P<0.05) of both carrageenan- and formalin-induced oedema in rat, guinea-pigs and mice (maximal inhibitions: 39.5, 45.0 and 48.6, respectively)[226].

The stem bark extract of *Mangifera indica* was evaluated for antipyretic activity in mice. The extract exhibited antipyretic effect in yeast-induced hyperpyrexia[227].

The analgesic activity of aqueous extract of *Mangifera indica* leaves (200 and 400 mg/kg) was studied in albino rats using hot plate and acetic acid induced writhing methods. *Mangifera indica* 200 and 400 mg/kg significantly increased (P<0.001) the reaction time in hot plate method at 120 minutes (8.96±0.12 and 10.61±0.2, respectively). Acetic acid induced writhing test showed a significant (P<0.001) decrease in number of writhes in *Mangifera indica* 200 and 400 mg/kg treated rats (43.76±1.59 and 30.33±1.41 respectively) in treated rats compared with control (67.17±0.75)[228].

2.72. Marrubium vulgare

Marrubiin, esterified derivatives, exhibited significant analgesic effect against the writhing test in mice. Marrubiinic acid showed better activity and excellent yield, and its analgesic effect was confirmed in experimental models of pain in mice[229].

The antinociceptive profile of marrubiin, the main constituent of this plant, was studied in some models of nociception in mice. Marrubiin exhibited potent and dose-related antinociceptive effects. ID_{50} was: 2.2 micromol/kg, ip, in the writhing test, 6.6 micromol/kg, ip, (first phase) and 6.3 micromol/kg, ip, (second phase) in the formalin-induced pain test and 28.8 micromol/kg, ip, in the capsaicin test[230-231].

The analgesic effects of the hydroalcoholic extract of *Marrubium vulgare* were investigated in different models of pain in mice. The extract exhibited significant analgesic activity, antagonizing chemically-induced acute pain, the effect which could be attributed to the presence of steroids and terpenes[232].

2.73. Matricaria chamomilla

The peripheral analgesic activity of the essential oil and aqueous extracts of aerial parts of *Matricaria chamomilla* was investigated using acetic acid induced writhing reflex test in mice, and acute central analgesic activity by tail immersion method in rats. The essential oil of *Matricaria chamomilla* (100, 200 and 300 mg/kg, orally) and aqueous extract (200, 400 and 600 mg/kg, orally) exhibited analgesic activity in both tested models. In the acetic acid-induced writhing model,

both extracts showed analgesic effect characterized by a reduction in the number of writhes when compared to the control and reference drug. For the tail immersion method essential oil exhibited significant analgesic activity at low dose of 200 mg/kg comparable to the aqueous extract at higher a dose of 600 mg/kg[233-234].

The analgesic activity of ethyl acetate and n-butanol extracts of *Matricaria chamomilla* was studied using writhing reflex test in mice in comparison with diclofenac sodium. The prepared extracts showed better analgesic activity than diclofenac sodium, diclofenac sodium, *n*-butanol extract of chamomile produced significantly less (1.7 ± 0.8) writhes than the ethyl acetate extract (9.2 ± 5.9)[235].

The analgesic effect of *Matricaria recutita* extract (10, 30 and 50 mg/kg, ip) in acute pain was investigated in mice in the presence and absence of sex hormones. *Matricaria recutita* extract increased analgesia time both in intact and gonadectomized male and female mice, but had no effect in the presence of pharmacological doses of testosterone (2 mg/kg, sc) in male mice, and estradiol benzoate (0.1 mg/kg, sc) and progesterone (0.5 mg/kg, SC) in female mice[236].

The antinociceptive effect of *Matricaria chamomilla* hydroalcoholic extract and morphine was studied in vincristine-induced peripheral neuropathy in mice. Administration of *Matricaria chamomilla* extract before formalin injection showed significant ($P<0.05$) decrease of pain responses in both phases. Administration of vincristine produced significant ($P<0.05$) increase in pain response in second phase of formalin test. Injection of the extract and vincristine together showed that the extract decreased the vincristine induced pain significantly ($P<0.05$)[237].

2.74. Melia azadirachta

The ethanolic extract of the leaves of *Melia azedarach* was tested for analgesic activity using acetic acid induced writhing test in mice. Ethanolic extract of the leaves demonstrated analgesic activity. The extract demonstrated 45.45% ($P<0.001$) and 67.05% ($P<0.001$) writhing inhibition at the doses of 250 and 500 mg/kg respectively in a dose dependent manner, which is comparable with standard diclofenac sodium 69.32% ($P<0.001$) at the dose of 25 mg/kg[238].

The antipyretic effect of the hydro-methanol extract of *Melia azedarach* leaves was investigated using the yeast induced pyrexia method in rabbits. At 500 mg/kg dose the extract showed significant ($P<0.0001$) reduction in yeast-induced elevated temperature as compared with that of standard drug paracetamol, whereas the extract dose 250 mg/kg was less effective when compared with higher dose ($P<0.05$)[239].

2.75. Melissa officinalis

The antinociceptive effect of the ethanolic extract of *Melissa officinalis* and rosmarinic acid in chemical was investigated in behavioral models of nociception. The extract (3-1000 mg/kg, orally), 1 h prior to testing, produced dose-dependent inhibition of acetic acid-induced visceral pain, with ID_{50} value of 241.9 mg/kg. In the formalin test, the extract (30-1000 mg/kg, orally) also caused significant inhibition of both, the early (neurogenic pain) and the late (inflammatory pain), phases of formalin-induced licking. The extract (10-1000 mg/kg,orally) also caused significant and dose-dependent inhibition of glutamate-induced pain, with ID_{50} value of 198.5 mg/kg. Rosmarinic acid (0.3-3 mg/kg, orally), 1 h prior, produced dose-related inhibition of glutamate-induced pain, with ID_{50} value of 2.64 mg/kg. The mechanisms of antinociceptive effect involved cholinergic systems and the L-arginine-nitric oxide pathway[240].

2.76. Mentha longifolia

The antipyretic and antinociceptive properties of *Mentha longifolia* leaf aqueous extract were investigated using lipopolysaccharide (LPS)-induced pyrexia in rats, and acetic acid and hot plate analgesia tests in mice. *Mentha longifolia* leaf aqueous extract significantly reduced the LPS- elicited pyrexia. *Mentha longifolia* leaf aqueous extract (6.25-100 mg/kg, ip) profoundly inhibited the writhes produced by 3% acetic acid and significantly ($P< 0.001$) delayed the hot plate reaction time in mice[241].

2.77. Mirabilis jalapa

The antinociceptive effect of leaf ethyl acetate fraction from *Mirabilis jalapa* (10mg/kg, po) was investigated in mice. The extract fraction caused marked reduction in the allodynia caused by complete Freund's Adjuvant-CFA, surgical incision and partial sciatic nerve ligation. However, the fraction did not alter the paw edema or the increase of IL-1β levels produced by CFA. The antinociceptive effect of the fraction was reversed by the pre-treatment of animals with the muscarinic receptor antagonists (atropine, 5mg/kg, sc) or nicotinic receptor antagonists (mecamylamine, 0.001mg/kg, sc.) receptors. The fraction did not alter *in vitro* acetylcholinesterase activity in blood or spinal cord

samples, but it reversed the increase in the acetylcholinesterase activity observed in the spinal cord samples from mice injected with CFA. Furthermore, the fraction did not alter the indicators of liver or kidney lesion[242].

The antinociceptive effect of *Mirabilis jalapa* crude hydroethanolic leaves and stems extracts from leaves and stems was investigated in pain models in mice. The crude hydroethanolic extract from leaves was more potent than the crude extract from stems to inhibit abdominal constrictions induced by acetic acid, with ID_{50} values of 5.5 (2.3-13.1) and 18.0 (11.3-28.5) mg/kg, respectively. Crude hydroethanolic leaves extract also possessed antinociceptive effect in the tail-flick test. Pre-treatment with naloxone did not modify the antinociceptive effect, but co-administration with atropine completely prevented it, which indicated that the antinociceptive effect might depend on the cholinergic system[243-244].

2.78. Momordica charantia

The analgesic effect of *Momordica charantia* was not affect by naloxone pretreatment, suggesting that opioid receptors were not involve in the analgesic effect of *Momordica charantia* [245]. The effects of Momordica charantia in reducing pain was studied in primary knee osteoarthritis patients. The patients with primary knee osteoarthritis patients underwent 3 months of *Momordica charantia* (500 mg capsule thrice daily) and placebo supplementation respectively. Pain and symptoms throughout the *Momordica charantia* supplementation period were assessed using Knee Injury and osteoarthritis outcome score and EQ-5D-3L Health questionnaire, while rescue analgesia intake throughout the period of supplementation was measured using analgesic score. After 3 months supplementation period, body weight, body mass index, and fasting blood glucose reduced significantly in the *Momordica charantia* group. There were also significant improvements in Knee Injury and osteoarthritis outcome score subscales and EQ-5D-3L dimension score, and reduction in analgesic score[246].

The antipyretic effect of the ethanolic extracts of *Momordica charantia* fruit (500 mg/ kg) was studied using yeast-induced pyrexia in rats. The antipyretic activity of *Momordica charantia* was postulated to be due to individual or combined action of bioactive constituents of the extract[247].

2.79. Morus alba

The analgesic effects of UP1304, (contains a standardized blend of extracts from the rhizome of *Curcuma longa* and the root bark of *Morus alba*), were studied in rats with carrageenan-induced paw edema. Statistically significant improvements in pain resistance with paw edema suppression were observed in animals treated with UP1304, when compared to vehicle-treated rats. Results from the highest dose of UP1304 (400 mg/kg) were similar to those achieved by ibuprofen treatment at 200 mg/kg. *In vitro*, UP1304 showed dose-dependent inhibition of the enzymatic activities of COX and LOX[248-249].

The anti-nociceptive effect of this *Morus alba* stem extract was determined by measuring hind limb weight bearing, as well as its cartilage protective effect was studied in the anterior cruciate ligament transection -induced rat model of osteoarthritis. Oral administration of *Morus alba* stem extract (56 and 560 mg/kg) significantly attenuated joint pain as indicated by a significant ($P<0.05$) increase in the values of percent weight borne on the operated hind limb for the osteoarthritis - induced groups that received *Morus alba* stem extract at 56 and 560 mg/kg compared to vehicle-treated osteoarthritis - induced group. It, also significant improved the Mankin score in rats treated with 560 mg/kg *Morus alba* stem extract[250].

The antipyretic effect of the leaves of *Morus alba* (LMA) after frost was better than that of before frost significantly on feverish rats. The antipyretic components of postfrost LMA were identified as citric acid derivative and tryptophan which may be the act synergistically[251].

2.80. Morus nigra

The antinociceptive properties of dichloromethane extract from leaves of *Morus* nigra were studied using the formalin, hot plate, and tail immersion tests as well as acetic acid-induced writhing in mice. The extract at test doses of 100 and 300 mg/kg, orally, possessed antinociceptive activity in all tests. At 300 mg/kg, orally, the extract possessed stronger antinociceptive effect than indomethacin (5 mg/kg, orally and morphine (10 mg/kg, orally)[252].

Morusin, the main prenylflavonoid in the *Morus nigra* root barks exhibited a promising antinociceptive effect by intraperitoneal administration. The antinociceptive activity may be attributed to the participation of the opioid system[253].

2.81. Musa paradisiaca

The analgesic efficacy of aqueous extract of leaves of *Musa paradisiaca* (250mg/kg, 1000 mg/kg) was evaluated in mice by hot plate reaction time and acetic acid induced writhing models. The extract possessed significant analgesic activity in both models, the these effects could be due to the presence of central and peripheral effects[254-255].

2.82. Myrtus communis

Antinociceptive activity aqueous and ethanolic extracts of *Myrtus communis* aerial parts was performed using hot plate and writhing tests. In hot plate test, the aqueous and ethanolic extracts showed significant antinociceptive activity that was inhibited by naloxone. The extracts also exhibited antinociceptive activity against acetic acid-induced writhing [256-257].

The bicyclic monoterpenoid myrtenal which was identified in the essential oils of *Myrtus communis* (5 %) was tested for analgesic effects in rodents models. Anti-nociceptive activity (30 mg/kg, ip) was tested in male ICR mice after single and repeated administration on two established experimental pain models - acetic acid writhing test and hot plate test. The bicyclic monoterpenoid myrtenal demonstrated significant anti-nociceptive properties (toward both peripheral and thermal pain)[258].

2.83. Nicotiana tabacum

The analgesic activities of the methanolic leaf extract (100, 200 and 300mg/kg, orally) of *Nicotiana tabacum* was evaluated using tail immersion, hot plate and acetic acid- induced abdominal constrictions or writhing in mice. *Nicotiana tabacum* extracts exhibited good level of antinociceptive actianalgesic effect, it significantly increased the pain reaction time or latency period in the mice in a dose dependent manner[259-260].

Nicotiana tabacum and indomethacin, significantly decreased the mean total number of abdominal constrictions or writhes in a dose dependent manner, the percentage protection of the abdominal constriction reflex was also increased at a dose of 300mg/kg of the extract. Methanolic leaf extract of *Nicotiana tabacum* showed significant analgesic effect, which could be attributed to both central and peripheral nociceptive mechanisms[261-262].

2.84. Nigella sativa

Nigella sativa oil (50–400 mg/kg, orally) dose-dependently attenuated the nociceptive responses in mice caused by the acute nociceptive stimuli thermal (hot-plate test) and mechanical (tail-pinch test), and the early phase of the chemical stimulus (formalin test) [263].

Thymoquinone and its para-benzoquinone analogues showed a significant reduction in the paw licking time of animals in two phases of the formalin test[264].

Aqueous and methanolic extracts of *Nigella sativa* extracts were found to elicit thermal and mechanical anti-hyperalgesic effects with the using of hot-plate and Randall-Selitto tests[265].

The ethanolic extract of *Nigella sativa* possessed antinociceptive effects against an acetic acid-induced writhing test in mice[266].

The analgesic and antipyretic effects of the aqueous extract of *Nigella sativa* was investigated in mice compared with aspirin. The extract produced significant increase in the hot plate reaction time in mice indicating analgesic effect, but it possessed no effect on yeast induced pyrexia[267].

2.85. Ocimum basilicum

The analgesic effects of *Ocimum basilicum* essential oil were assessed in various mouse experimental pain models using formalin, acetic acid, heat, and carrageenan as stimuli. The essential oil was administered by intraperitoneal injection or inhalation. The involvement of various pathways in the analgesic effect of the essential oil was assessed by pretreating mice with selective pharmacological inhibitors. Th essential oils exerted analgesic effects in all pain models. Pretreatment with naltrindole, naloxone, or L-arginine significantly reduced the analgesic effects of the oils in the formalin test. The essential oils increased mean withdrawal latencies in a thermal plantar test at a high dose, but not at lower doses, while, they possessed no effect on motor coordination [268-269].

The analgesic effect of the methanolic extract of *Ocimum basilicum* was evaluated by tail immersion method in mice. The extract at a dose of 200 mg/kg, possessed analgesic comparable to the analgesic effect of aspirin[270].

2.86. Olea europaea

The methanolic extract of defatted fruits of *Olea europaea* at the 600 mg/kg dose and the aqueous extract at the 450 and 600 mg/kg doses inhibited pain induced in the second phase of formalin test. The anti-nociception by aqueous olive extract was not reversed by naloxone, which indicates that the opioid receptors are not involved in the analgesic effects of the extracts[271-272].

2.87. **Ononis spinosa**

The analgesic activity of a water extract of *Ononis spinosa* was studied in mice. Analgesic activity was investigated on the pain thresholds measured with the tail-flick test at 30, 90 and 150 min. The extract of *Ononis spinosa* showed analgesic activity equivalent to aspirin at 30 and 90 min, and even higher than aspirin at 50 mg/kg. At a dose of 100 mg/kg, *Ononis spinosa* extract possessed analgesic effect equivalent to aspirin at all time points[273].

The analgesic effect of ethanolic *Ononis spinosa* root extract was evaluated using phenylquinone writhing test in mice. The extract reduced reaction to pain by up to 80% at doses of 100 and 500 mg/kg, intraperitoneally. However, no analgesic effect was observed after oral administration and no analgesic effect was observed in the hot plate test in mice after oral and intraperitoneal administration of the extract[274-275].

TRPM3 (melastatin-related transient receptor potential 3) was blocked by ononetin, a deoxybenzoin from *Ononis spinosa. By this inhibition it* attenuate thermal nociception[276].

2.88. Onopordum acanthium

The analgesic and antipyretic activities of butanolic extract of *Onopordum acanthium* were studied using 20 % brew yeast injection induced pyretic model, and 1 % acetic acid induced analgesic model in rats. Butanolic extract 200 and 400 mg/kg significantly decreased acetic acid-induced abdominal writhes compared to standard aspirin. Butanolic extract also showed dose and time dependent decrease in body temperature in yeast induced pyrexia, comparable to standard, aspirin[277].

Origanum vulgare

The analgesic effect of aqueous leaf extract of *Origanum vulgare* (84 mg/kg, po) was studied using tail flick method in mice. In tail flick method, *Origanum vulgare* showed significant increase in the reaction time after 30 min of administration as compared to control group[278-279].

The possible involvement of GABA- ergic mechanism in analgesic effect of aqueous extract of *Origanum vulgare* (ORG) was studied in a rat model of acute pain test. Rats were cannulated into the left ventricle, 5-7days after the recovery from surgery, the extract was intraventricularly injected at dose of 3 µg/rat icv, baclofen (10 mg/kg, ip), CGP35348 (100 nmol/kg, icv), muscimol (1 mg/kg, ip) and bicuculline (5 mg/kg, ip) were separately injected 20 min before the injection of the extract. The response latency of rats to thermal stimulation was recorded using Tail-Flick test. Injection of the extract resulted in a significant and dose-dependent increase in the response latency, there was also a significant increase in the response latency after co-administration of the extract with baclofen compared with control group, while, co-administration of the extract/bicuculline, caused significant decrease in the response latency which indicated that the antinociception of the extract might be mediated, at least in part, by GABA receptors[280].

The antinociceptive effect of intracerebroventricular microinjection of *Origanum vulgare* extract was investigated in rats, with the studying of possible involvement of opioid receptors. The co- administration of the extract with morphine showed a significant increase in tail flick latency, while, naloxone, pretreatment significantly inhibited the antinociceptive activity of the extract and morphine[281].

The antinociceptive effect of combined *Achillea millefolium* (31.6, 100, 178, and 316 mg/kg) and *Origanum vulgare* extract (5.6, 10, 17.8, and 31.6 mg/kg), encapsulated in liposome administered ip, was assessed using 3% formalin test in rat. The interaction index and isobolographic analysis revealed a synergistic effect of the extracts. Naloxone also reduced the antinociceptive effect of the liposome encapsulated co-administered extract[282].

2.89. Oxalis corniculata

The ethanolic extract of *Oxalis corniculata* (200 and 400mg/kg) was evaluated for antinociceptive effect in rats with diabetic neuropathy. Diabetic rats showed significant reduction in tail flick latency (49%) in hot water tail immersion test and decreased paw withdrawal by 40% in hot plate test by the end of 5th week[283].

The analgesic activity of the ethanolic extract of whole *Oxalis corniculata* was evaluated by using acetic acid-induced writhing method, hot plate method and tail immersion test. The percentage inhibition of writhers or percentage protection were found to be 44% and 47% for extract at a dose 100 and 300 mg/kg, respectively, in the acetic acid-induced writhing method ($P<0.01$). The percentage increase in reaction time at 60 minutes were 166% and 200% for extract at a dose of 100 and 300 mg/kg, respectively, in hot plate method ($P<0.001$). The percentage increase in reaction time at 60 minutes were 120% and 240% at a dose of 100 and 300 mg/kg, respectively in tail immersion test ($P<0.01$, $p<0.001$)[284].

2.90. Peganum harmala

The analgesic activities of *Peganum harmala* seeds extracts (aqueous, alcoholic, chloroform, petroleum ether and ethyl acetate) 200 mg/kg, orally, were evaluated using glacial acetic acid induced writhing in mice. The ethyl acetate, followed by alcohol and chloroform extracts showed significant analgesic activities[285].

The analgesic effect of the alkaloid extract of *Peganum harmala* was investigated by writhing, formalin, and hot plate tests in mice. The alkaloid extract (12.5 and 25mg/kg) in a dose-dependent manner significantly reduced the nociception by acetic acid. The extract also significantly reduced the painful stimulus in both phases of formalin test ($P<0.001$). In addition, the extract produced significant increase of the reaction time in hot plate test. Studying of mechanism of analgesic effect indicated that the alkaloid extract possessed both central and peripheral antinociceptive activities which may be mediated by opioid receptors[286].

The analgesic effect of the total alkaloid extract was studied in formalin- induced pain response in mice. Alkaloid extract possessed significant dose dependently (28.63-100%) reduction in pain response compared to control. The observed responses in both phases were dose- dependent with ED_{50} of 27.87 and 24.63 mg/kg respectively[287].

Intraperitoneal administration of the *Peganum harmala* extract produced significant and dose- dependent hypothermia. Harmine and harmaline, the major constituents of the *Peganum harmala* alkaloid, also lowered the body temperature. In studying of the mechanism of hypothermia by pretreatment with many blockers, it appeared that the *Peganum harmala* alkaloids produce hypothermic effect mainly through endogenous 5-HT stimulation of 5-HT1A receptor[288].

2.91. Polygonum bistorta (Bistorta officinalis)

The analgesic effect of *Polygonum bistorta* water extract, was studied in comparison with morphine and amidazofen in mice. *Polygonum bistorta* water extract possessed marked analgesic effect, the analgesic intensity was close to that of amidazofen and morphine. Naloxone, resisted the analgesic effect of morphine but not that of *Polygonum bistorta* water extract, which gave an indication that the analgesic effect of the extract was not mediated by opiate receptor[289].

The analgesic effect of *Polygonum bistorta* water extract (0.10 and 0.15 mg/g) was investigated in mcie. The extract showed very significant analgesic effect on the writhing reaction induced by acetic acid in mice. It also possessed marked analgesic effect on the pain caused by hot-plate. Naloxone didn't reverse the analgesic effect of the extract on the pain caused by hot-plate. Compared with the control group, the exerted very significant analgesic effect on the pain caused by electric stimulation[290].

2.92. Portulaca oleracea

The effects of hydroalcoholic seed extract of *Portulaca oleracea* on pain threshold measured using tail flick test, was investigated in male mice. Increased pain threshold was recorded 30 and 60 minutes after administration of moderate and high dose of the extract[291].

10% ethanolic extract of *Portulaca oleracea v. sativa* possessed analgesic effect in rats. The anti-nociceptive activity of the extract was attenuated by naloxone pre-treatment indicating the involvement of opioid receptors in its anti-nociceptive effects of the extract(76). The 10% ethanolic extract of the aerial parts of *Portulaca oleracea* possessed significant analgesic after intraperitoneal and topical but not oral administration compared with diclofenac sodium[292].

2.93. Potentilla reptans

The analgesic effect of hydroalcoholic extract of *Potentilla reptans* (25, 50 and 100 mg/kg) was investigated in rats. Writhing, formalin and tail-flick tests were used to evaluate the analgesic effects of the extract. The results revealed that *Potentilla reptans* possessed significant analgesic effect and the opioid pathway seemed to be involved in the analgesic effect of the extract[293].

2.94. Prunus armeniaca

The pain-relieving activity of amygdalin (0.1, 0.5, 1.0, and 10.0 mg/kg), was investigated in pain induced in rats through intraplantar injection of formalin. The intramuscular injection of amygdalin significantly reduced the formalin-induced tonic pain in both early and late phases. During the late phase, amygdalin reduced the formalin-induced pain in a dose-dependent manner. Molecular analysis targeting c-Fos and inflammatory cytokines such as TNF-α and IL-1β also showed a significant effect of amygdalin, which matched the results of the behavioral pain analysis[294].

2.95. Prunus mahaleb

The antinociceptive effect of *Prunus mahaleb* (powder dissolved in distilled water and given orally as 1, 5, 3, 12, 24 mg/kg) was investigated by using hot-plate test in mice. *Prunus mahaleb* at (3, 12, 24) mg/kg produce analgesic effects and increased in threshold of pain. The pain reaction time was increased after 2 min and the maximum analgesic effect after 10 min of oral *Prunus mahaleb* administration in dose (3, 12, 24) mg/kg and the duration of analgesia last from 2 min to 20 min[295].

2.96. Punica granatum

Antinociceptive activity of the methanol extract of fruit peels of Amrouz variety (MoEA) and methanol extract of fruit peels of Sefri variety (MoES) was examined using four models of pain (writhing, formalin, intra-cerebroventricular injection, hotplate and tail-immersion tests)**.** In the writhing test, the index of pain inhibition (IPI) was 52% for MoEA (150 mg/kg, ip) and 29% for MoES (150 mg/kg, ip). In the formalin test, the IPI of early and late phase were, 75% and 82%, respectively for MoEA (100 mg/kg, ip) and 8% and 63% for MoES (100 mg/kg, ip). In the hot plate and tail-immersion test, MoEA and MoES increased in a dose dependent manner the reaction latency to the thermal stimuli. MoEA was more potent than MoES [296].

2.97. Quercus infectoria

The analgesic activity of the methanol extract of the galls of *Quercus infectoria* (20 mg/kg, ip) was investigated in rats using hot plate and tail-flick methods. The methanol extract exhibited significant analgesic activity in the tail-flick model by increasing the reaction time of the rats to 8.0 sec at 30 min after treatment in comparison to control (4.4 sec). In the tail-flick model, the extract and sodium salicylate demonstrated comparable analgesic effect[297].

2.98. Rhus coriaria

The analgesic effect of hydro alcoholic leaf extract of *Rhus coriaria* (80, 100 and 300 mg/kg, ip), was investigated in a rat by using writhing, tail flick and formalin tests. All dose levels of the extract inhibited the number of contractions induced by acetic acid in the writhing test significantly. None of the dose levels of the extract showed antinociceptive activity in the formalin test except the dose of 100 mg/kg (at chronic phase) and the dose of 300 mg/kg (at chronic-acute phase). In the tail flick model, the highest effect was recorded at the dose of 300 mg/kg of the extract. Utilization of naloxone plus extract inhibited the antinociceptive effect of the extract, indicating that the analgesic effect for the extract may be mediated via both peripheral and central mechanisms[298].

2.99. Ricinus communis

The analgesic effects of the mixture of *Lawsonia inermis* leaves with aqueous extract of *Ricinus communis* were investigated in male rats with an induced knee osteoarthritis as a model of chronic pain by intra-articular injection of mono sodium iodoacetate (MIA). Analysis of mechanical allodynia (after 21 days), hotplate latency test (after 10 days), spontaneous movements (after 7 days) showed significant analgesic effects[205].

The antipyretic and antinociceptive activities of *Ricinus communis* leaves hydroalcoholic extracts (150, 250 and 500mg/kg) were tested in rats. The antipyretic activity, was studied by using Brewer's yeast suspension to induce hyperthermia. Antinociceptive activity was investigated by using acetic acid-induced abdominal writhing, formalin-induced paw licking reflex and heat-induced pain models. The extract significantly lowered rectal temperature in a dose-dependent manner from 1h to 4h of study. *Ricinus communis* extract showed a dose-dependent reduction in abdominal

writhing induced by acetic acid and decreased the paw licking reflex in formalin-induced nociceptive response. In the heat test, *Ricinus communis* extract exhibited significant analgesic effects evidenced as an increase in latency time[299].

2.100. Rosa damascena

The nociception effect of the ethanolic extract of the flowering tops of *Rosa damascena,* was studied by using acetic acid-induced writhing in mice. The extract significantly and dose dependently suppressed the frequency of acetic acid induced writhing in mice. At the dose 250 mg/ kg the extract of *Rosa damascena* showed 37.07% writhing inhibition where as at 500 mg/ kg produced 49.07 % writhing inhibition[300].

A non-randomized clinical trial, on 80 elderly patients was carried out to determine the effect of the aromatherapy with the Damask rose (performed 24 hours after surgery and there were 4 sessions within 2 hours with 30 minutes interval) on pain of elderly patients after knee arthroplasty surgery. The study demonstrate that aromatherapy has a positive effect on reducing the postoperative pain of the elderly[301].

A double-blind, placebo-controlled cross-over trial was performed on patients with migraine headache to evaluate the effect of topical formulation of *Rosa damascena* oil on migraine headache. The patients were treated for the first 2 consecutive migraine headache attacks by topical *Rosa damascena* oil or placebo. Mean pain intensity of the patients' migraine headache was not significantly different. Additionally, regarding mean scores of nausea and/or vomiting, photophobia, and phonophobia severity of the patients, no significant differences between the two groups were observed. Finally, applying syndrome differentiation model, the mean score of migraine headache pain intensity turned out to be significantly lower in patients with "hot" type migraine syndrome at in 30, 45, 60, 90, and 120 min after *Rosa damascena* oil application compared to "cold" types[302].

2.101. Saccharum officinarum

Methanol fraction of *Saccharum officinarum* juice and the major flavone, tricin-7-*O*-(2″- α-L-rhamnopyranosyl)-α-D-galacturonide, significantly inhibited nociceptive responses in mice. The isolated flavone inhibited strongly the neurogenic phase in formalin test without interfering with the inflammatory one. The co-administration of the opioid antagonist, naloxone, significantly reversed the antinociceptive effects on the neurogenic phase of both methanol fractions and the isolated flavone, demonstrating the involvement of the opioid system on the antinociceptive effect[303].

2.102. Salix species

Analgesia: salicylate alleviate mild-to-moderate pain. They are less effective than opioids, and they are more effective against pain associated with integumental structures (pain of muscular and vascular origin, arthritis, and bursitis) than with pain associated with the viscera. Antipyresis: salicylate reduce elevated body temperature with little effect on normal body temperature[304-305].

A prospective open-label study was carried out on 12 patients with migraine without aura (IHS criteria). Twelve weeks treatment with a combination product of *Tanacetum parthenium* 300 mg and *Salix alba* 300 mg (salicin content ≥ 1.5%) twice daily was administered to investigate the effects on migraine attack frequency (primary outcome parameter), intensity and duration (secondary outcome parameters). Attack frequency was reduced by 57.2% after 6 weeks and 62.6% at 12 weeks in 9 out of 10 patients (no significant improvement between 6 and 12 weeks) with 70% of patients having a reduction of at least 50%. Attack intensity was reduced by 38.7% after 6 weeks and 62.6% after 12 weeks in 10 out of 10 patients, with 70% having a reduction of at least 50%. Attack duration decreased by 67.2% after 6 weeks and 76.2% after 12 weeks in 10 out of 10 patients. Two patients were excluded for reasons unrelated to treatment. No adverse events were recorded[306].

A 2-month randomized non-cross over study in 82 patients with chronic arthritis pain showed a small but statistically significant improvement in pain symptoms and less sufferers from osteoarthritis with a low dosage of herbal medicine (containing 100 mg *Salix alba* extract, guaiacum, black cohosh, sarsaparilla and poplar bark) compared to placebo[307].

2.103. Salvia aegyptiaca

The analgesic and antipyretic effects of the crude acetone and methanol extracts of *Salvia aegyptiaca* were tested in mice. The extracts caused dose-related inhibition of acetic acid-induced abdominal constriction, and significantly reduced formalin-induced pain. Treatment with the extracts at doses of 0.5 and 1 g/kg significantly increased the reaction time in the hot-plate test. Treatment with both extracts did not significantly affect the rectal temperature of normothermic mice. The methanol extract (0.5 and 1.0 g/kg) did not affect the rectal temperature of hyperthermic mice,

but the acetone extract was effective in significantly reducing the rectal temperature of hyperthermic mice, 0.5 and 1 h after administration of the extract at doses of 0.25-2 g/kg[308].

2.104. Sambucus ebulus

The chronic (formalin test) and acute (tail flick) pain models of rats were carried out to evaluate the analgesic effect of *Sambucus ebulus* rhizome extract. Extract at a dose of 300 mg/kg (ip) had no effect on tail flick latency, while 100 and 200 mg/kg ip of extract increased this latency ($P<0.01$ and $P<0.001$, respectively). In formalin test, the extract at a dose of 300 mg/kg ip alleviated the animals' nociception in the second phases. The extract at a dose of 200 mg/kg showed a significant effect on both phases ($P<0.001$), which was not reversed by naloxone (2 mg/kg ip)[309].

2.105. Schinus molle

The antinociceptive capacities of the *Schinus molle* fruit extract were assessed *in vitro*. The extract presented an interesting antinociceptive capacities[310].

Dried seeds of *Schinus molle* were extracted by hexane, acetyl acetate and dichloromethane. The dichloromethane extract was separated into two fractions (1 and 2) by column chromatography. Both factions were tested for their analgesic effects. The two fractions significantly increased ($P<0.05$) the tail flick latency, fraction 2 provided better and more long lasting protection against thermal pain[311].

The analgesic effect of the dichloromethanol extract of *Schinus molle* was investigated in *in vivo* models. This extract showed low acute toxicity, and analgesic effect. Following further fractionation, the hexane/dichloromethane (75/25) fraction showed significantly reduced the threshold of pain to chemical stimulus[312].

2.106. Sesbania sesban (syn: Sesbania aegyptiaca)

The petroleum ether, chloroform, ethyl acetate, ethanol, and water extracts (50 and 100 mg/kg, ip) of *Sesbania sesban* were screened for antinociceptive activity using hot plate test and acetic acid-induced writhing test in mice. Petroleum ether, chloroform, and ethyl acetate extracts showed significant and dose-dependent activity in both tests. The antinociceptive action of the extracts was blocked by naloxone, suggesting involvement of opioid receptors in the action[313].

2.107. Sisymbrium sophia (Syn: Descurainia sophia)

Antipyretic effect was determine in hyperthermia induced by subcutaneous injection of Brewer's yeast in rats. While, analgesic activity was investigated by using writhing method in mice. The antipyretic activity of *Descurainia sophia* is nearly the same as diclofenac sodium in a dose of 400 mg/kg. *Descurainia sophia* extract possessed analgesic activity compared with the control and paracetamol. Small dose of (70%) alcoholic extract produced 20% protection against writhing induced by p-benzoquinone while high dose produced 40% protection [314].

The antinociceptive activity of *Descurainia Sophia* seeds essential oil was evaluated using the formalin induced paw licking test. Administration of *Descurainia sophia* seeds essential oil (100 and 300 mg/kg) exerted significant ($P<0.05$) anti-nociceptive action in phase I (neurogenic phase). The essential oil also was found to exert significant ($P<0.01$) antinociceptive activity in Phase 2 (inflammatory-mediated phase), at all concentrations tested. The nociceptive effect was partly mediated via the modulation of channel signaling pathway as well as the activation of vanilloid, dopamine, and cannabinoid-receptors[315].

2.108. Solanum dulcamara

The analgesic effects of *Solanum dulcamara* stem essential oil (300 mg/kg) were studied in male mice with the using of writhing (assessment of abdominal contractions), Tail Flick (assessment of tail jump duration), and formalin (assessment of pain associated with sole of foot). Using of 300 mg/kg essential oil in writhing tests (decreased from 41 in control to 13) and tail flick (increased from 2.8±0.2 seconds in control group to 6.1±0.5 seconds) showed significant analgesic effect ($P<0.01$)[316].

2.109. Sonchus oleraceus

The antinociceptive effect of hydroethanolic and dichloromethane extracts of the aerial parts of *Sonchus oleraceus* was studied in mice using the formalin, hot plate, and tail immersion tests as well as acetic acid-induced writhing test. The extracts (30-300 mg/kg, orally) produced significant inhibitions on chemical nociception induced by intraperitoneal acetic acid and subplantar formalin since decreased the number of writhing episodes and the time licking. Treatment

with the extracts in the same doses produced a significant increase of the reaction time in tail immersion and in the hot plate test. The extracts administered at 300 mg/kg, orally showed antinociceptive effect stronger than indomethacin (5 mg/kg, orally) and morphine (10mg/kg,orally)[317-318].

2.110. Spartium junceum

The antinociceptive effect of the hydroalcoholic extract of the flowers of *Spartium junceum* (10, 20, 30 and 40 mg/kg) was studied in mice by using formalin test. The extract exerted analgesic effect in both early and late phases. The high dose of the extract possessed antinociceptive effect equal to morphine 3mg/kg[319].

2.111. Stachys lavandulifolia

The antinociceptive effects of *Stachys lavandulifolia* essential oil (25 or 50mg/kg, orally) and (-)-α-bisabolol (25 or 50mg/kg, orally), its main compound, were studied in algogen-induced orofacial nociceptive behavior in mice. **Oral** treatment with essential oil and α-bisabolol displayed significant inhibitory effects in different orofacial pain tests in mice, but α-bisabolol proved to be more effective, significantly reducing nociceptive behavior in all tests including both phases of the formalin test [320].

The analgesic effects of hydroalcoholic extract (100, 200 and 400 mg/kg, ip) of *Stachys lavandulifolia* was studied in mice using the formalin and tail immersion tests. The results showed that all doses of *Stachys lavandulifolia* extract (100, 200 and 400 mg/kg), significantly ($P<0.001$) reduced the licking time in mice, both in acute and chronic phases of formalin test, compared to the control groups[321].

2.112. Stellaria media

The analgesic effect of the methanolic extract of *Stellaria media* leaf was studied using acetic acid-induced writhing, hot plate and tail flick tests in mice. The extract at 300 mg/kg produced significant ($P<0.05$) inhibition of the acetic acid-induced abdominal constrictions in mice. The analgesic property of the extract was also exhibited in the tail flick test. The extract significantly ($P<0.05$) increased the tolerance of the mice to pain relative to indomethacin-treated mice[322].

The analgesic effect of the ethanolic extract of *Stellaria media* was studied using hot plate analgesic model in mice. The ethanolic extract (500mg/kg) showed a potent analgesic property which is slightly higher than the 10mg/kg of diclofenac sodium[323].

2.113. Taraxacum officinale

Taraxacum officinale extract was confirmed in rats as an alternative to paracetamol in inflammatory and painful cases without biochemical and reproductive side effects [324].

2.114. Teucrium chamaedrys

The aqueous leaves extract of *Teucrium chamaedrys* (50–200 mg/kg) produced significant inhibition of the second phase response in the formalin pain model, while only the high dose (200 mg/kg) of the extract showed an analgesic effect in the first phase. The extract also inhibited acetic acid-induced abdominal writhes in a dose-dependent manner. The tail flick latency was dose dependently enhanced by the extract [325].

2.115. Teucrium polium

The analgesic effect of total extract and essential oil of *Teucrium polium* was studied using writhing test, a visceral pain model in mice. The total extract in doses of 150 mg/kg (39.13%, $P<0.001$), 225 mg/kg (65.44%, $P<0.001$), 300 mg/kg (21.41%, $P<0.01$) induced reduction in writhing response as compared to control with the ED_{50} 67.92 mg/kg. The essential oil in doses of 9.37 mg/kg (35.22%, $P<0.001$), 18.75 mg/kg (59.63%, $P<0.001$), 37.5 mg/kg (86.60%, $P<0.001$), 75 mg/kg (90.22%, $P<0.001$) and 150 mg/kg (78.58%, $P<0.001$) induced significant reduction in writhing response when compared to control with the ED_{50} of 29.41 mg/kg. The extract free from essential oil was prepared and injected into mice at a dose of 225 mg/kg in order to ensure the importance of essence in production of visceral antinociception. The antinociception, was reduced from 65.44 to 49.85% ($P<0.001$)[326].

The analgesic effect of *Teucrium polium* leaf aqueous extract (100 and 200 mg/kg/day, ip, for 2 weeks) in streptozotocin induced diabetic rat was studied by using formalin test. *Teucrium polium*-treated diabetic rats exhibited a lower nociceptive score as compared to untreated diabetics. Extract caused significant lower nociceptive scores in both phases

of the formalin test. Diabetic animals receiving *Teucrium polium* extract showed also a less intensive nociceptive behavior, especially in the first phase[327].

The anti-nociceptive effect of different doses (30-240 mg/kg) of *Teucrium polium* aqueous extract was determined by hot-plate test in mice. The *Teucrium polium* extract increased reaction time dose-dependently (P<0.01 for all doses). However the anti-nociceptive effect of extract was significantly less than that of morphine[328].

The antipyretic effect of the ethanolic extract of the flowering tops of *Teucrium polium* was investigated in rats. The extract was effective against both yeast and carrageenin pyrexia in rats[329].

2.116. Thuja occidentalis

The methanolic extracts of whole plant of *Thuja occidentalis*, were studied for antipyretic activity by TAB (Typhoid) vaccine and PGE1 induced pyrexia in rabbits. In TAB vaccine-induced fever, the fever was significantly reduced and the body temperature was normalized by administration of 100 and 200 mg/kg dose orally and the activity was comparable to paracetamol. Pyrexia induced by PGE1 was significantly reduced as compared to aspirin[330].

2.117. Thymus kotschyanus

The ethanolic extract of the aerial part of *Thymus kotschyanus* (50, 100 and 200 mg/kg, ip) was evaluated for the analgesic effect by using formalin test and tail flick test. The extract at doses of 100 mg/kg (P<0.05) and 200 mg/kg (P<0.001) induced analgesia in the early and late phases of the formalin test. Maximum analgesia in acute and late phases was recorded at a dose of 200 mg/kg, while at a dose of 50 mg/kg, the extract was ineffective. The extract at a dose of 200 mg/kg increased the antinociceptive activity in minutes 30 (P<0.01), 45, 60 and 75 (P<0.05) after formalin injection and also in tail-flick test in comparison to control[331].

2.118. Tribulus terrestris

The analgesic effect of methanolic extract (suxheletion and percolation) of *Tribulus terrestris* was investigated in male albino mice by formalin and tail flick test. Both extracts (100 mg/kg, ip) showed highly significant analgesic effect compared to the control group (P<0.01) in formalin and tail flick test. The analgesic effect of the extract was lower than morphine, 2.5 mg/kg in both tests, and higher than aspirin 300 mg/kg in chronic phase of pain in formalin test (P<0.05). Pretreatment of animal with naloxone did not change the analgesia induced by the plant extract in both tests, therefore the analgesic effect of the extract didn't mediated by opioid receptor. The ulcerogenic study indicated that the gastric ulcerogenecity of plant extract was lower than the indomethacin in the rat's stomach[332].

The analgesic activity of flavonoids fraction was determined by acetic acid-induced writhing response in mice. Flavonoids fraction (12.5, 25 and 50 g RMM/kg) decreased writhing times with a dose-dependent manner. Compared with the aspirin group, 25 g RMM/kg of flavonoids fraction exhibited similar analgesic effect, while, the analgesic intensity of 50 g RMM/kg of flavonoids fraction was stronger than aspirin group (P< 0.05)[333].

2.119. Trifolium pratense

The isoflavones methanol extract from *Trifolium pratense* was administered orally (500 mg/kg) to ovariectomized (OVX) and normal (controls) rats for 90 and 180 days. Their pain threshold was monitored using tail flicking and formalin test methods. Observations showed that the OVX rat pain threshold was reduced due to estrogen deprivation, whereas the pain threshold levels in OVX rats treated with isoflavones extract was similar to the control animals[334].

2.120. Trigonella foenum-graecum

The antinociceptive effects of *Trigonella foenum-graecum* leaves extract were investigated by using tail-flick and formalin tests. Intraperitoneal administration of 500 mg/kg of the extract and 100 did not show any effect in the tail-flick test, but the 1000 and 2000 mg/kg of the extract produced significant increase in the tail-flick latency. The extract (500 mg/kg, ip) demonstrated antinociception only in the first phase, but 1000 and 2000 mg/kg, ip alleviated the pain in both phases[335].

2.121. Tropaeolum majus

The ethanolic and aqueous leaf extract of *Tropaeolum majus* (200 and400 mg/kg) were investigated for analgesic activity by tail immersion (rats), hot plate (rats) and writhing method (mice). By all models the extracts possessed significant analgesic effect (P<0.05)[336].

2.122. Utrica dioica

The antinociceptive effect of *Urtica dioica* leaf hydroalcoholic extract was studied in mice by using acetic acid-induced writhing and formalin test. The extract dose-dependently reduced acetic acid-induced abdominal twitches. In formalin test, the extract at all doses (100, 200, and 400 mg/kg) didn't suppress the licking behavior of first phase while doses of 200 and 400 mg/kg significantly inhibited the second phase of formalin test337].

The analgesic and antipyretic activities of the aqueous extracts of *Urtica dioica* were evaluated in mice by use of formalin–induced writhing test. Antipyretic activity was investigatd by using Brewer's yeast induced pyrexia. The aqueous leaf extracts of *Urtica dioica* reduced pain, and fever mostly at dose 150 mg/kg[338].

The water extract of *Urtica dioica* was studied for analgesic properties. The inhibitor effects of the extract (50, 100and 200 mg/kg) on the acetic acid-induced writhing in mice Were 62.1, 70.4 and 89.2%, respectively[339].

The analgesic properties of the ethanolic extracts of the leaves of *Urtica dioica* was analysed by hot plate method, formalin test, acetic acid-induced writhing test and the tail-flick test with different doses. In all tests, the leaf's ethanolic extract exhibited significant analgesic activity ($P<0.001$) at a dose of 400 mg/kg[340].

Twelve week randomized, placebo-controlled double-blind parallel- study was carried out to investigate the efficacy and safety of MA212 [special formulation composed of rosehip (*Rosa canina*) puree/juice concentrate, nettle (*Urtica dioica*) leaf extract, and devil's claw (*Harpagophytum procumbens* or *Harpagophytum zeyheri*) root extract, with vitamin D] in patients with gonarthritis. The mean pre-post change of the Western Ontario and McMaster Universities Arthritis Index pain score was 29.87 in the MA212 group and 10.23 in the placebo group. Compared to placebo, both physical and mental quality of life significantly improved with MA212. There was a trend towards reduced analgesics consumption with MA212, compared to placebo[341].

A clinical trial was performed to determine the effect of common stinging nettle in the treatment of joint pain. Eighteen self-selected patients using the nettle sting of *Urtica dioica* were interviewed. All except one respondent were sure that netles had been very helpful and several considered themselves cured. No observed side effects were reported, except a transient urticarial rash[342].

2.123. Viola odorata

A randomized placebo controlled clinical trial, was performed on 41 febrile children to determine the efficacy of *Viola odorata* oil (20 drops, rubbed on the peripheral margin of the patient umbilicus) for fever control in febrile neutropenic children. The mean temperature reduced significantly in the viola group after 30 minutes of administration, while there was no significant change in the placebo group. The number of patients who received paracetamol as the rescue treatment was significantly lower in the viola group than that in the placebo group[343]. The aqueous ($P<0.01$) and methanolic ($P<0.05$) extract of *Viola odorata* at a dose level of 400 mg/kg, orally showed a significant analgesic effect in the peripheral and central models of pain (tail immersion and hot plate method) in rtas, while n-hexane and butanolic extracts did not show any significant effect ($P>0.05$)[344]. A randomized, double blind, placebo-controlled clinical trial was performed on 88 patients to determine the effectiveness of a combination of (*Viola odorata* flowers, *Rosa damascena* flowers and *Coriandrum sativum* fruits, 500 mg capsules three times a day and propranolol 20 mg tablet twice a day), on severity, duration and frequency of migraine headaches. At the end of the 4^{th} week treatment, the combination was effective in improving headaches in patients with migraine[345].

2.124. Vitex angus-castus

The antinociceptive activity of *Vitex agnus castus* fruit decoction was measured by using acetic acid writhing test. At 200 mg/kg, it exhibited a higher analgesic activity (81.68%) than acetylsalicylic acid used as a positive control (74.35%)[346].

The antinociceptive effects of essential oil extracted from *Vitex agnus-castus* (EOVAC) leaves were investigated using tail immersion test, formalin test, and acetic acid-induced visceral pain in rats in adult male rats. The essential oil (sc) and morphine (ip) significantly ($P<0.05$) reduced pain responses in both formalin and tail immersion tests. Pretreatment with naloxone or atropine significantly ($P<0.05$) reversed the essential oil-induced analgesia in both formalin and tail immersion tests. Moreover, the essential oil and piroxicam produced significant ($P<0.05$) inhibition in the acetic acid-induced writhing response. The results indicated that endogenous opioidergic system as well as muscarinergic receptors may be involve in the antinociceptive activity of *Vitex agnus-castus* essential oil[347].

2.125. Ziziphus spina-christi

The antinociceptive effect of the aqueous extract of *Zizyphus spina-christi* root bark was investigated in mice and rats. Acetic acid-induced writhing, formalin and thermal (hot plate) tests were used. The extract (50 and 100 mg/kg, ip) showed a dose-dependent analgesic effect in all the tests used[348].

A fraction from the methanol extract of *Zizyphus spina-christi* root bark was studied for analgesic effect (25, 50 and 100 mg/kg, ip) on chemical (acetic acid-induced writhing, formalin), mechanical (analgesy-meter) and thermal (tail-flick) in rats and mice. The fraction showed dose related analgesic effect on all the models except the tail-flick test in which the activity was not significant[349].

3. Conclusion

The current review highlighted the medicinal plants possessed analgesic and antipyretic effects with special focus on their mode of action, as promising future drugs because of their safety and effectiveness.

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